

AHRQ Comparative Effectiveness Review

Surveillance Program

CER # 21:

Comparative Effectiveness of In-Hospital Use of Recombinant Factor VIIa for Off-Label Indications vs. Usual Care

Original release date:

May, 2010

Surveillance Report:

February, 2012

Key Findings:

- KQ1: is not applicable for the assessment of updating status
- KQ2: 1 of 3 conclusions is possibly out of date
- KQ3 (a , b): 3 of 13 conclusions are possibly out of date
- KQ4 (b.i, b.ii, c) are uptodate, and in (a) 1 of 2 conclusions is possibly out of date
- Expert opinion: One of the 2 experts stated that the conclusions for KQ2 and KQ4 were not still valid
- No FDA alerts

Summary Decision:

This CER's priority for updating is **LOW**

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None of the investigators has any affiliation or financial involvement that conflicts with material presented in this report; however, one of the experts was a member of the CONTROL Steering Committee (this trial was funded by Novo Nordisk).

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1. Introduction

The purpose of this mini-report was to apply the methodologies developed by the Ottawa and RAND EPCs to assess whether or not the CER No. 21 (Comparative Effectiveness of In-Hospital Use of Recombinant Factor VIIa for Off-Label Indications vs. Usual Care)¹ is in need of updating. This CER was originally released in June, 2010. It was therefore already due for a surveillance assessment. When the Surveillance program began in the summer of 2011, this CER was selected to be in the second wave of reports to go through the assessment.

This CER included 74 publications identified by using searches through August 4, 2009 and addressed four key questions to evaluate the level of evidence currently available to support the effectiveness and safety of using recombinant activated coagulation factor VII (rFVIIa) for clinical indications beyond those approved by the Food and Drug Administration (FDA). The purpose of this report is two-fold: (1) To profile the full range of clinical indications for which rFVIIa is being used and the types of studies available to evaluate these uses, and (2) To provide a comparative effectiveness review of rFVIIa versus usual care for several clinical indications: intracranial hemorrhage, massive bleeding secondary to trauma, and the selected surgical procedures of cardiac surgery, liver transplantation, and prostatectomy. The key questions of the original CER were as the following:

1. Indications, Populations, and Characteristics of Comparative Studies of Off-Label rFVIIa Use?
2. Use of rFVIIa for Selected Indications in Patient With/Undergoing Intracranial Hemorrhage?
3. Use of rFVIIa for Selected Indications in Patient With/Undergoing Massive Bleeding from Trauma?
- 4a. Use of rFVIIa for Selected Indications in Patient With/Undergoing Liver Transplantation ?
- 4b. Use of rFVIIa for Selected Indications in Patient With/Undergoing Cardiac Surgery ?
- 4c. Use of rFVIIa for Selected Indications in Patient With/Undergoing Prostatectomy ?

Key Questions 2-4. For each of these clinical areas we will answer the following questions:

- a. Does the use of rFVIIa reduce mortality and disability compared to usual care?
- b. Are there patient subpopulations more likely to benefit from rFVIIa use?
- c. Does rFVIIa use increase thrombosis-related events?
- d. Are there patient subpopulations where harms are more likely?
- e. Which patient subpopulations experience net benefits of rFVIIa and does this vary by timing and dosage?

The conclusion(s) for each key question are found in the executive summary of the CER report.¹

2. Methods

We followed *a priori* formulated protocol to search and screen literature, extract relevant data, and assess signals for updating. The identification of an updating signal (qualitative or quantitative) would be an indication that the CER might be in need of updating. The Food and Drug Administration (FDA) surveillance alerts received from the Emergency Care Research Institute (ECRI) were examined for any relevant material for the present CER. The clinical expert opinion was also sought. Taken into consideration the totality of evidence (i.e., updating signals, expert opinion, FDA surveillance alerts), a consensus-based conclusion was drawn whether or not any given conclusion warrants any updating (up to date, possibly out of date, or out of date). Based on this assessment, the CER was categorized into one of the three updating priority groups: high priority, medium priority, or low priority. Further details on the Ottawa EPC and RAND methods used for this project are found elsewhere.²⁻⁴

2.1 Literature Searches

The CER search strategies were reconstructed in Ovid MEDLINE (R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R), Embase, and EBM Reviews - Cochrane Central Register of Controlled Trials using the OVID platform and in BIOSIS Previews using the Web of Knowledge platform as per the original search strategies appearing in the CER's Appendix A.¹ All searches were limited to 2008 to present (Jan 4th, 2012). The syntax and vocabulary, which include both controlled subject headings (e.g., MeSH) and keywords, were applied according to the databases indicated in the appendix and in the search strategy section of the CER report. The MEDLINE, Embase and BIOSIS searches were limited to five general medical journals (Annals of Internal Medicine; BMJ; JAMA; Lancet; and New England Journal of Medicine) and five specialty journals (Journal of Trauma® Injury, Infection and Critical Care; NeurocriticalCare; Annals of Thoracic Surgery; Transplantation; and Stroke). Restricting by journal title was not possible in the Cochrane search and pertinent citations were instead selected from the results. Further details on the search strategies are provided in the Appendix A of this mini-report.

2.2 Study Selection

All identified bibliographic records were screened using the same inclusion/exclusion criteria as one described in the original CER¹.

2.3 Expert Opinion

In total, 10 experts (7 experts who had either served as part of the technical expert panel for and/or peer reviewed the original report and 3 local experts) were requested to provide their feedback in a provided their opinion/feedback in a pre-specified matrix table on whether or not the conclusions as outlined in the Executive Summary of the original CER were still valid.

2.4 Check for Qualitative and Quantitative Signals

All relevant reports eligible for inclusion in the CER were examined for the presence of qualitative and quantitative signals using the Ottawa EPC method (see more details in Appendix B). CERs with no meta-analysis were examined for qualitative signals only. For any given CER that included a meta-analysis, the assessment started with the identification of qualitative signal(s), and if no qualitative signal was found, this assessment extended to identify any quantitative signal(s). The identification of an updating signal (qualitative or quantitative) would be an indication that the CER might be in need of updating. The definition and categories of updating signals are presented in Appendix B and publications.²⁻⁴

2.5 Compilation of Findings and Conclusions

All the information obtained during the updating process (i.e., data on qualitative/quantitative signals, the expert opinions, and FDA surveillance alerts) was collated and summarized. Taken into consideration the totality of evidence (i.e., updating signals, expert opinion, and FDA surveillance alerts) presented in a tabular form, a conclusion was drawn whether or not any conclusion(s) of the CER warrant(s) updating.

Conclusions were drawn based on four category scheme:

- Original conclusion is still **up to date** and this portion of CER does not need updating
- Original conclusion is **possibly out of date** and this portion of CER may need updating
- Original conclusion is **probably out of date** and this portion of CER may need updating
- Original conclusion is **out of date** and this portion of CER is in need of updating

In making the decision to classify a CER conclusion into one category or another, we used the following factors when making our assessments:

- If we found no new evidence or only confirmatory evidence and all responding experts assessed the CER conclusion as still valid, we classified the CER conclusion as still up to date.

- If we found some new evidence that might change the CER conclusion, and /or a minority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as possibly out of date.
- If we found substantial new evidence that might change the CER conclusion, and/or a majority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as probably out of date.
- If we found new evidence that rendered the CER conclusion out of date or no longer applicable, we classified the CER conclusion as out of date. Recognizing that our literature searches were limited, we reserved this category only for situations where a limited search would produce prima facie evidence that a conclusion was out of date, such as the withdrawal of a drug or surgical device from the market, a black box warning from FDA, etc.

2.6 Determining Priority for Updating

Determination of priority groups (i.e., Low, Medium, and High) for updating any given CER was based on two criteria:

- How many conclusions of the CER are up to date, possibly out of date, or certainly out of date?
- How out of date are the conclusions (e.g., consideration of magnitude/direction of changes in estimates, potential changes in practice or therapy preference, safety issue including withdrawn from the market drugs/black box warning, availability of a new treatment)

3. Results

3.1 Update Literature Searches and Study Selection

A total of 177 bibliographic records were identified (MEDLINE=46, Embase=100, CENTRAL=8, and BIOSIS=23). After de-duping, 76 records remained (MEDLINE=33, Embase=38, and CENTRAL=0, and BIOSIS=5), of which 43 records were deemed potentially eligible for full text screening. Of the 43 full text records, 10 were included in the update.⁵⁻¹⁴ We also included two reviews of RCTs^{15,16} and three observational reports¹⁷⁻¹⁹ that were identified by one of the experts who contributed in this report. Thus, a total of 15 publications were included in the report.⁵⁻¹⁹

3.2 Signals for Updating in Newly Identified Studies

3.2.1 Study overview

The study, population, treatment characteristics, and results for the 15 included publications are presented in Appendix C (Evidence Table).

Six of the 15 included publications were randomized placebo-controlled trials (RCTs)^{5,7,8,10,11,13}, 2 were systematic reviews of RCTs^{15,16}, and 7 were observational studies.^{6,9,12,14,17-19} The length of the follow-up across the studies ranged from 2 years¹⁴ to 9 years⁹. The sample size of the randomized trials ranged from 169¹³ to 1,397⁵. The sample size of the observational comparative studies ranged from 24¹⁷ to 2,050 participants¹².

The population consisted of patients with intracranial hemorrhage in 3^{5,9,10} of the 15 included reports, patients with trauma in 8 of the publications^{5,7,8,11-14,19}, patients undergoing cardiac surgery in 3 of the reports^{5,6,17}, and patients with liver transplantation in 1 of the reports¹⁵. No publication was identified on patients undergoing prostatectomy. The age of patients in these publications ranged from 24- 76 years old with majority having younger ages; 7 of the studies were consisting of participants with age 24 - ≤50.9 years old^{5,7,8,12-14,19}. One report focused on children 0-18 years old¹⁸, and one review included all age groups.¹⁶

The doses of rFVIIa used in these studies varied from 5-360 µg/kg of patient weight^{5-7,9,10,14-17}. The majority of the participants in these reports were male ranging from 48.6%⁹ to 95%¹⁷.

The majority of the studies reported direct outcomes: 8 reported thromboembolic events^{5,6,9-12,14,16}, 8 reported mortality^{8,11-16,19}, and 2 reported acute respiratory distress syndrome^{11,12}.

3.2.2 Qualitative signals

See also Table 1 (Summary Table), Appendix B, and Evidence Table (Appendix C)

Key question #1

Indications, Populations, and Characteristics of Comparative Studies of Off-Label rFVIIa Use?

This key question was not applicable for the assessment of updating status of the CER.

Key Question # 2

Use of rFVIIa for Selected Indications in Patient With/Undergoing Intracranial Hemorrhage?

Atrial Thromboembolic Event (TE):

1. The lack of evidence in the original CER was supplemented with the finding from an identified publication demonstrating association of Arterial TEs with higher dose of rFVIIa: Receiving 80 µg/kg rFVIIa versus 20 µg/kg and placebo: OR=2.14; 95% CI: 1.09, 4.41; P=0.031.¹⁰ **1 Signal (A6)**
2. The findings from two identified publications were in agreement with the original CER demonstrating increased number of atrial thromboembolic events in rFVIIa group:
 - a. In rFVIIa versus Placebo groups, the OR was 1.67 with 95% CI: 1.03, 2.69; p=0.04.⁵ **No Signal**
 - b. In rFVIIa (20 µg/kg), 80 µg/kg, and placebo groups the number (%) of atrial thromboembolic events were 47 (26%), 82 (46%) and 49 (27%) respectively with p=0.04.¹⁰ **No Signal**

Key Question # 3a

Use of rFVIIa for Selected Indications in Patient With/Undergoing Massive Bleeding from Trauma (Body Trauma)

Thromboembolic Event: (rFVIIa versus placebo)

1. The findings from an identified report showed a non-significant association for rFVIIa use: OR: 1.39; 95% CI: 0.69, 2.77; p= 0.36.⁵ **No Signal**
2. The findings from another publications demonstrated n (%) of TE : 47 (100) vs. 40 (100); p=NR.¹¹ **No Signal**

Mortality: (rFVIIa use versus placebo)

1. The findings from an identified report was in agreement with the original CER showing no significant difference in 30-day mortality: n(%): 32 (12.2) vs. 31 (11.1); p= 0.61.¹¹ **No Signal**
2. In agreement to the original CER, the finding from another report demonstrated: mortality rate of 20.0% in rFVIIa arm versus 14.3% in No rFVIIa group, p>0.05. However, the same study demonstrated significantly increased mortality rate with the use

of rFVIIa in regression analysis: OR: 1.67, 95% CI: 1.08, 2.60; p=0.02.¹² **1 Signal** (Other)

3. The finding from another report was in agreement with the original CER demonstrating no difference in 30-day mortality rate between the two arms for patients with blunt trauma (11.0% versus 10.7%, p= 0.93) and for patients with penetrating trauma (18.2% versus 13.2%, p= 0.40).⁷ **No Signal**
4. In conflict with the original CER finding, one retrospective study demonstrated that 24-hour mortality rate was significantly reduced in patients who received ≥ 30 units of packed red blood cells (26% in rFVIIa group versus 64% in No rFVIIa group; p=0.02).¹⁹ **1 Signal** (Other)

Red Blood Cell (RBC) Requirement: The findings from identified reports were in agreement with the original CER demonstrating inconsistent results:

1. In rFVIIa versus No rFVIIa, one report demonstrated the number (range) of RBC unites: 10 (6–16) versus 10(4–17); p<NS.¹² **No Signal**
2. In rFVIIa versus placebo, the rFVIIa arm used significantly reduced unites of RBC in blunt trauma patients: (mean \pm SD) 48 hours: 7.8 ± 10.6 versus 9.1 ± 11.3 ; p= 0.04 but non significantly reduced unites of RBC in penetrating trauma patients: 48 hours: 5.0 ± 7.4 versus 6.8 ± 6.9 ; p= 0.11.⁷ **No Signal**
3. In rFVIIa versus no rFVIIa groups, one observational study reported the mean transfusion requirement (packed RBC) to be: 35.6 ± 2.6 vs. 25.6 ± 0.7 ; p=0.001 at 6-hour transfusion, and 38.6 ± 2.9 vs. 28.0 ± 1.0 ; p=0.001 at 24-hour transfusion.¹⁹ **No Signal**

Key Question # 3b

Use of rFVIIa for Selected Indications in Patient With/Undergoing Massive Bleeding from Trauma (Brain Trauma) i.e., Traumatic Brain Injury [TBI])?

Atrial Thromboembolic Event:

1. The findings was in agreement with the original CER, demonstrating no effect on atrial TE in rFVIIa versus placebo was 2/61(3.3%) versus 1/36 (2.8%).⁵ **No Signal**
2. In another report, there were no TE events in both rFVIIa versus no rFVIIa arms.¹⁴ **No Signal**

Mortality: In agreement with the original CER findings, there was no significant difference between rFVIIa versus no rFVIIa groups: n=7(50%) vs. n=4(29%); p=0.22.¹⁴ **No Signal**

Red Blood Cell Requirement: There was a significant reduction of RBC use in patients receiving rFVIIa versus no rFVIIa group for the median (range) of packed red blood cells use in 1) preoperative: 0 (0–2) versus 4 (2–8); p= 0.001; 2) intraoperative: 1 (0–2) versus 5 (2–8); p=0.002; 3) postoperative: 1 (0–2) versus 3 (2–5); p= 0.002; and 4) total: 4 (1–5) versus 14 (10–17); p= 0.001.¹⁴ **1 Signal** (Other)

Key Question # 4a

Use of rFVIIa for Selected Indications in Patient With/Undergoing Liver Transplantation?

Mortality: The finding from a meta analysis of RCTs was in agreement with the original CER demonstrating no significant difference between the groups (rFVIIa vs. Placebo): OR=0.96, 95% CI: 0.35, 2.62.¹⁵ **No Signal**

Red Blood Cell Requirement: The finding from a meta analysis of RCTs was in conflict with the original CER demonstrating no significant difference between the groups (rFVIIa vs. Placebo): mean difference: 0.32, 95% CI: -0.08, 0.72.¹⁵ **1 Signal (A1)**

Key Question # 4b.i

Use of rFVIIa for Selected Indications in Patient With/Undergoing Cardiac Surgery (Adult Cardiac Surgery)?

Atrial Thromboembolic Event: Only 1 publication was identified that demonstrated no significant effect on atrial TE for rFVIIa use versus placebo: OR=1.59, 95% CI: 0.47, 5.34; p=0.45.⁵ **No Signal**

Operating Room Time: Only 1 observational study reported lesser median operating room time for rFVIIa group versus reoperation for refractory bleeding after surgery group. The data were not reported; p<0.05.¹⁷ **No Signal**

Key Question # 4b.ii

Use of rFVIIa for Selected Indications in Patient With/Undergoing Cardiac Surgery (Pediatric Cardiac Surgery)?

Mortality, TE and Transfusion requirement: Only 1 publication was identified and it demonstrated similar results to the original CER showing no significant effect on mortality, rate of TE (8% versus 4%; p=NR) and transfusion requirement (93.2 mL/kg versus 108.3 mL/kg; p=0.225) in rFVIIa use versus placebo groups.⁶ **No Signal**

Key Question # 4c

Use of rFVIIa for Selected Indications in Patient With/Undergoing Prostatectomy?

No publication was identified. **No Signal**

3.2.3 Quantitative signals

See also Table 1 (Summary Table), Appendix B, and Evidence Table (Appendix C)

The presence of quantitative signals (B1 and B2) was checked only if none of the studies identified through the update search indicated a qualitative signal.

The data pooling was not possible for key questions # 4bi and #4 bii because no new study eligible for meta-analysis and no data for meta-analysis were available to check for quantitative signals for # 4bi and # 4bii respectively.

3.3 FDA surveillance alerts

No FDA alerts was identified.

3.4 Expert opinion

Two of the 10 contacted clinical experts (one CER-specific and one local expert) provided their responses/feedback in the matrix table (Appendix D). The responses from one expert was in agreement with the conclusions outlined in the executive summary of the CER demonstrating the conclusions to be still valid. He was aware of some additional publications that were included in this report. However, another expert's opinion was in conflict with the original CER findings for two questions indicating the conclusions for questions 2 and 4 not to be still valid.

4. Conclusion

Summary results and conclusions according to the information collated from different sources (updating signals from studies identified through the update search, FDA surveillance alerts, and expert opinion) are provided in Table 1 (Summary Table). Based on the assessments, this CER is categorized in **Low** priority group for updating.

Key Question # 1

Key question 1 was not applicable for the assessment of updating status

Key Question # 2

Signals from studies identified through update search: i) Only 1 of 3 qualitative signals was identified. **1 Signal (A6).**

Experts: One of the two experts stated that conclusions in the key question # 2 were not still valid.

FDA surveillance alerts: No alert was identified.

Conclusion: **1 of 3 conclusions is possibly out of date**

Key Question #s 3a and 3b

Signals from studies identified through update search: In total 3 qualitative signals were identified for questions # 3a and # 3b. **3 Signals (3 Other)**

Experts: Both of experts stated that conclusions in the key question # 3 were still valid.

FDA surveillance alerts: No alert was identified.

Conclusion: **3 of 13 conclusions are possibly out of date**

Key Question #s 4a , 4bi, 4bii and 4c

Signals from studies identified through update search: Only 1 signal was identified for #4a. No publications were identified for # 4c. No signal was identified for # 4bi and # 4bii. **1 Signal (A1)**

Experts: One of the two experts stated that conclusions in the key question # 4 were not still valid.

FDA surveillance alerts: No alert was identified.

Conclusion: **1 of 2 conclusions is possibly out of date for # 4a, but the conclusions for (4b.i; 4b.ii and 4c) are uptodate.**

Summary Table (rFVIIa)

[illegible]

<p>moderate strength of evidence with good applicability for treatment use in the population targeted by the RCTs—patients with intracerebral hemorrhage who were not on anticoagulation therapy. In all cases where meta-analyses were performed, the results of the risk difference and arcsine metrics were consistent. The risk difference summary statistics are reported below. Regarding the benefits and harms of rFVIIa, our findings include: (Figure C).</p> <ul style="list-style-type: none"> There was no effect of rFVIIa on mortality (risk difference: low-dose group: 0.031 (95 percent CI -0.086 to 0.024), medium-dose group: 0.020 (95 percent CI -0.076 to 0.036), high-dose group: 0.027 (95 percent CI -0.121 to 0.068); <i>p</i> value of the <i>Q</i> statistic for all risk differences is 0.248) (also see Figure C: each circle represents a study; larger circles correspond to larger studies; shaded circles represent studies on treatment use of rFVIIa, and white circles represent studies on prophylactic use of rFVIIa). rFVIIa use also did not reduce the rate of poor functional outcome as measured on the modified Rankin Scale (risk difference: low-dose group: 0.024 (95 percent CI -0.093 to 0.045), medium-dose group: 0.029 (95 percent CI -0.099 to 0.041), high-dose group: 0.040 (95 percent CI -0.154 to 0.075); <i>p</i> value of the <i>Q</i> statistic for all risk differences is 0.088). <u>There was an increased rate of arterial thromboembolic events with rFVIIa use</u> vs. usual care for the medium- and high-dose groups (risk difference: low-dose group: 0.025 (95 percent CI -0.004 to 0.053), medium-dose group: 0.035 (95 percent CI 0.008 to 0.062), high-dose group: 0.063 (95 	<p><u>placebo</u></p> <p>Atrial Thromboembolic Event: n(%) 47 (26%) , 82 (46%) vs. 49 (27%); <i>p</i>=0.04</p> <p>Venous Thromboembolic Event: Similar across groups</p> <p>However, Arterial TEs were associated with: <u>Receiving 80 µg/kg rFVIIa</u>: OR=2.14; 95% CI: 1.09, 4.41; <i>P</i>=0.031 (compared to 20 µg/kg and placebo)</p> <p><u>Signs of cardiac or cerebral ischemia at presentation:</u> OR=4.19; 95% CI: 1.03, 1.27; <i>P</i>=0.010)</p> <p><u>Age:</u> OR=1.14/5 years; <i>P</i>=0.0123</p> <p><u>Prior use of antiplatelet agents:</u> OR=1.83; 95% CI: 1.04, 3.20; <i>P</i>=0.035</p>		<p>publicatoin (Stein, et al.) that was excluded from this update because it was already included in the original CER. He said, “Regarding OAT, I believe there is now substantial evidence that rFVIIa will rapidly reverse anticoagulation in these patients, although documentation of changed outcomes is still needed. Look for the work of Stein, et al. in the J of Trauma. At least one of these papers described an economic benefit to the use of FVIIa in patients with TBI. “</p>
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<p>percent CI 0.011 to 0.063); <i>p</i> value of the <i>Q</i> statistic for all risk differences is 0.277) (see Figure D).</p> <ul style="list-style-type: none"> • rFVIIa use significantly decreased the percent relative hematoma expansion (standardized mean difference: low-dose group: 0.146 (95 percent CI -0.291 to -0.001), medium-dose group: 0.240 (95 percent CI -0.385 to 0.095), high-dose group: 0.334 (95 percent CI -0.579 to -0.090); <i>p</i> value of the <i>Q</i> statistic for all risk differences is 0.840). • In summary, current evidence of moderate strength suggests that neither benefits nor harms substantially exceed each other for rFVIIa use in the ICH subgroup of intracranial hemorrhage. <p>Regarding subpopulations of patients, our findings include:</p> <ul style="list-style-type: none"> • Earlier administration of rFVIIa for ICH may increase benefits, but this finding may be confounded by earlier CT scanning among these patients. • There may be greater benefits in younger patients with smaller initial hematoma size. • There was no evidence of a dose effect for any endpoint. • Evolution of intracranial hemorrhage management may reduce the size of the population in which there is a potential benefit of rFVIIa. <p>There were insufficient studies to assess the impact of rFVIIa on patients taking oral anticoagulation therapy</p>						
Key question # 3a: Use of rFVIIa for Selected Indications in Patient With/Undergoing Massive Bleeding from Trauma (Body Trauma)						
There were two RCTs (both published in a single paper and of <i>fair</i> quality) and three	1 RCT⁵	No Signal	See	No Alerts	Both of the expert said	2 of 9

<p>with higher baseline pH, shorter time to administration, and higher platelet counts.</p> <ul style="list-style-type: none"> There was inadequate information available to assess the effect of rFVIIa dosage. 	<p>1 RCT ⁷</p>	<p>Mortality Rate (propensity matched): % 20 vs. 14.3; p=NS</p> <p>However, Multivariate Regression of Variables Associated With Overall Mortality: <u>RFXVIIa use:</u> OR: 1.672, 95% CI: 1.079, 2.593; p=0.022 Complications rate: 21% vs. 21%;p=NS RBC Use: [value(range)] 10 (6–16) vs. 10(4–17); p<NS</p> <p>No Signal The findings are in agreement with the original CER findings: <u>rFVIIa vs. placebo</u></p> <p>Blunt Trauma: n(%) 30-d mortality: 24 (11.0) vs. 26 (10.7); p= 0.93 Durable morbidity: 19 (8.7) vs. 23 (9.5); p= 0.75</p> <p>Penetrating Trauma: n(%) 30-d mortality: 8 (18.2) vs. 5 (13.2); p= 0.40 Durable morbidity: 1 (2.3) vs. 0; p= 1.00</p> <p>RBC Requirement <u>Blunt Trauma: (mean±SD)</u> <u>24 hours:</u> 6.9±10.4 vs. 8.1 ± 10.9; p= 0.04 <u>48 hours:</u> 7.8 ± 10.6 vs.</p>				
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	1 Non RCT ¹⁹	<p>9.1±11.3; p= 0.04</p> <p><u>Penetrating Trauma</u> <u>24 hours:</u> 4.5±7.3 vs. 6.2±6.5; p= 0.11 <u>48 hours:</u> 5.0±7.4 vs. 6.8 ± 6.9; p= 0.11</p> <p>1 Signal (Other) The finding from this observational study was in conflict with the original CER findings for mortality demonstrating: 24-hour Mortality in patients required ≥30 unites of packed RBC: rFVIIa vs. No rFVIIa 26% vs. 46%; p=0.02</p> <p>Mean Transfusion Requirement (packed RBC): 6-hour Transfusion: 35.6±2.6 vs. 25.6±0.7; p=0.001 24-hour Transfusion: 38.6±2.9 vs. 28.0±1.0; p=0.001</p>				
Key question # 3b. Use of rFVIIa for Selected Indications in Patient With/Undergoing Massive Bleeding from Trauma (Brain Trauma) i.e., Traumatic Brain Injury [TBI])						
There was one RCT (<i>fair</i> quality) and one comparative observational study (<i>fair</i> quality) with a total of 79 patients who received rFVIIa. This yielded low strength of evidence with fair applicability for treatment use in the population targeted—patients with intracranial hemorrhage secondary to TBI who were not on anticoagulation therapy. Regarding the benefits and harms of rFVIIa, our findings include:	1 RCT ⁵	<p>No Signal</p> <p>The findings is in agreement with the original CER:</p> <p><u>rFVIIa vs. placebo</u></p> <p>Atrial Thromboembolic Event: No./total no. (%) 2/61(3.3) vs. 1/36 (2.8)</p>	See above	No Alerts	Both of the expert said the conclusion for this question was still valid.	1 of 4 conclusions are possibly out of date

<ul style="list-style-type: none"> There was no effect of rFVIIa on mortality (Figure C) or thromboembolic event rate (Figure D). rFVIIa use vs. usual care had no effect on hematoma growth but, in the one study that evaluated it, reduced the time to neurosurgical intervention (e.g., by normalizing the INR to an acceptable level). Current evidence of low strength is too limited to compare harms and benefits. <p>Regarding subpopulations of patients, our findings include:</p> <ul style="list-style-type: none"> Patients with coagulopathy may have increased benefits. Patients experiencing blunt trauma to the cerebral vessels may have a greater risk of thromboembolic events when rFVIIa is used. There was inadequate information available to assess the effect of rFVIIa dosage. 	1 Non RCT ¹⁴	<p>1 Signal (Other) The findings is in agreement with original CER (traumatic brain injury who presented coagulopathic): <u>rFVIIa vs. no rFVIIa</u></p> <p>Mortality: n(%) 7*(50) vs. 4(29); p=0.22 * though four deaths were secondary to withdrawal of care according to patient and family wishes</p> <p>Thromboembolic complication: <u>0 vs. 0</u> However,</p> <p>Packed red blood cells (PRBC) usage [(median value (range))]: PRBC preoperative 0 (0–2) vs. 4 (2–8); p= 0.001 PRBC intraoperative 1 (0–2) vs. 5 (2–8) ; p=0.002 PRBC postoperative 1 (0–2) vs. 3 (2–5); p= 0.002 PRBC total 4 (1–5) vs. 14 (10–17); p= 0.001</p>				
Key question # 4a: Use of rFVIIa for Selected Indications in Patient With/Undergoing Liver Transplantation						
There were four RCTs (two <i>fair</i> quality, two <i>poor</i> quality) and one comparative observational study (<i>fair</i> quality) with 215 patients who received prophylactic rFVIIa at initiation of liver transplantation. This yielded low strength of evidence with fair applicability for prophylactic use in the population targeted—patients with cirrhosis of Child’s class B or C. Regarding the benefits and harms of rFVIIa, our findings	1 Review of RCTs ¹⁵	<p>1 Signal</p> <p>The findings from this meta analysis is in agreement for the mortality, but in conflict for the RBC requirement with the original CER findings:</p>	See above	No Alerts	One of the experts said the conclusion for this question was still valid and he was aware of the following additional report: “Chavez-Tapia NC et al. Prophylactic activated recombinant	1 of 2 conclusions is possibly out of date

<p>include:</p> <ul style="list-style-type: none"> There was no effect of rFVIIa use on mortality (Figure C) or thromboembolism (Figure D) relative to usual care. There was a trend across studies toward reduced RBC transfusion requirements with rFVIIa use vs. usual care. Neither operating room time nor ICU length of stay were reduced with rFVIIa use compared to usual care. Current evidence of low strength is too limited to compare harms and benefits. <p>Regarding subpopulations of patients, our findings include:</p> <ul style="list-style-type: none"> Patients who refuse blood product transfusions, such as Jehovah's Witnesses, may experience benefits from rFVIIa use, but there was inadequate information to assess this. There was inadequate information available to assess the effect of rFVIIa dosage. 		<p><u>rFVIIa vs. Placebo</u></p> <p>Mortality: OR; 95% CI 0.96; 0.35, 2.62</p> <p>red blood cells units: MD; 95% CI 0.32; -0.08,0.72</p>			<p>factor VII in liver resection and liver transplantation: systematic review and meta-analysis. PLoS One. 2011;6(7):e22581"</p> <p>However, the other expert said the conclusion for this question was not still valid.He commented, "My sense is that use in this area has plateaued at a relatively infrequent rate of use, primarily for rescue." However, he didn't rferecned any publication.</p>	
Key question # 4b.i. Use of rFVIIa for Selected Indications in Patient With/Undergoing Cardiac Surgery (Adult Cardiac Surgery)						
<p>There were two RCTs (one <i>good</i> quality, one <i>fair</i> quality) and four comparative observational studies (two <i>good</i> quality, two <i>fair</i> quality) with 251 patients receiving rFVIIa. One of the RCTs assessed prophylactic rFVIIa use, whereas the rest of the studies evaluated treatment use. These yielded a moderate strength of evidence for the outcome of thromboembolic events but a low strength of evidence for the remainder of the outcomes. The studies had fair applicability for rFVIIa use in the population targeted—patients undergoing cardiac surgery, including</p>	1 RCT⁵	<p>No Signal</p> <p>The findings is in agreement with the original CER:</p> <p>rFVIIa vs. placebo</p> <p>Atrial Thromboembolic Event:</p> <p>OR: 1.59; 95% CI: 0.47, 5.34; p= 0.45</p>	No new study eligible for meta-analysis is available to check	No Alerts	<p>One of the experts said the conclusion for this question was still valid and he was aware of one additional report: "Uber WE et al. Administration of recombinant activated factor VII in the intensive care unit after complex</p>	The conclusion is uptodate

<p>straightforward procedures (e.g., isolated coronary artery bypass grafting [CABG]) and more complex procedures (e.g., ascending aortic dissection repair).</p> <p>In all cases where meta-analyses were performed, the results of the risk difference and arcsine metrics were consistent. The risk difference summary statistics are reported below. Regarding the benefits and harms of rFVIIa, our findings include:</p> <ul style="list-style-type: none"> • There was no effect of rFVIIa on mortality (risk difference 0.007; 95 percent CI -0.049 to 0.063; <i>p</i> value for the <i>Q</i> statistic is 0.63) (also see Figure C). • <u>rFVIIa use was associated with a higher thromboembolic event rate (risk difference 0.053; 95 percent CI 0.01 to 0.096; <i>p</i> value for the <i>Q</i> statistic is 0.99) (also see Figure D).</u> • RBC transfusion needs were possibly reduced with rFVIIa, but the trend was only apparent across the higher quality studies that reported on this outcome (one RCT and one <i>good</i> quality cohort study, <i>p</i> = 0.11 and <i>p</i><0.001, respectively; the other RCT only reported on total transfusion needs, which were significantly reduced). The findings across the <i>fair</i> quality observational studies were conflicting. • There were conflicting results among studies regarding ICU length of stay. • Current evidence of moderate strength (for thromboembolic events) or low strength (for all other outcomes) suggests that neither benefits nor harms substantially exceed each other. <p>Regarding subpopulations of patients, our findings include:</p>	<p>1 Non RCT ¹⁷</p>	<p>No Signal</p> <p>rFVIIa vs. reoperation for refractory bleeding after surgery: <u>Median Operating room time:</u> Significantly less (Values:NR) ;p<0.05</p>	<p>the quantitative signal.</p>	<p>cardiovascular surgery: clinical and economic outcomes. J Thorac Cardiovasc Surg. 2011 Jun;141(6):1469-77”</p> <p>However, the other expert said the conclusion for this question was not still valid. He commented, “My sense is that use in this area has plateaued at a relatively infrequent rate of use, primarily for rescue.” However, he didn’t reference any publication.</p>	
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<ul style="list-style-type: none"> There was a suggestion that earlier treatment use of rFVIIa increases its benefits. There was inadequate information available to assess the effect of rFVIIa dosage. 						
Key question # 4b:ii . Use of rFVIIa for Selected Indications in Patient With/Undergoing Cardiac Surgery (Pediatric Cardiac Surgery)						
<p>A total of 40 patients received rFVIIa prophylaxis in one <i>poor</i> quality RCT, (the only included study). This yielded an insufficient strength of evidence and fair applicability for the population targeted—infant patients with congenital heart defects requiring surgical repair. Regarding the benefits and harms of rFVIIa, our findings include:</p> <ul style="list-style-type: none"> There were no data reported on mortality from the single RCT available. The effect of rFVIIa on thromboembolic events cannot be discerned from existing data due to limited events. RBC transfusion requirements demonstrated a nonsignificant decrease among patients receiving rFVIIa vs. usual care: 77 mL and 127 mL, respectively, $p = 0.15$. Time from end of cardiopulmonary bypass to chest closure was increased significantly in rFVIIa patients: 99 minutes (SD = 27) for rFVIIa vs. 55 minutes (SD = 29) for usual care, $p = 0.03$. Current evidence is insufficient for comparing harms and benefits. <p>Regarding subpopulations of patients, our findings include:</p> <ul style="list-style-type: none"> Patients on extracorporeal membrane oxygenation (ECMO) may be more likely to 	1 Non RCT ⁶	<p>No Signal</p> <p>For the harm analysis, the findings from a non-comparative observational study was: <u>rFVIIa vs. matched controls</u></p> <p>rate of thrombosis 8% vs 4%; $p = \text{NR}$</p> <p>Mortality: No difference</p> <p>Median total transfusion volume: 93.2 mL/kg vs. 108.3 mL/kg; $p = 0.225$</p>	No data for meta-analysis was available to check for quantitative signal	No Alerts	One of the experts said the conclusion for this question was still valid; however, the other expert said the conclusion for this question was NOT still valid. Further comment was not provided.	The conclusion is up to date

<p>experience thromboembolic events.</p> <ul style="list-style-type: none"> There was inadequate information available to assess the effect of rFVIIa dosage. 						
Key Question 4c. Use of rFVIIa for Selected Indications in Patient With/Undergoing Prostatectomy						
<p>There was one <i>fair</i>-quality RCT on prophylactic use of rFVIIa in 24 patients undergoing prostatectomy. This yielded an insufficient strength of evidence and poor applicability for the population targeted—patients undergoing retropubic prostatectomy for prostate cancer or benign hyperplasia but not on anticoagulation therapy. These data have limited relevance given the major changes in usual care since the RCT was performed and the lack of reported use of rFVIIa for prostatectomy in the United States in 2008. Regarding the benefits and harms of rFVIIa, our findings include:</p> <ul style="list-style-type: none"> Mortality and thromboembolic events could not be evaluated due to limited reported events (one thromboembolic event in a rFVIIa patient, no deaths in either group). RBC transfusion needs were significantly decreased by rFVIIa, with a possible greater effect at higher doses: 1.5 units (SD = 0.4) for usual care, 0.6 units (SD = 0.3) for 20 mcg/kg, 0 (0) for 40 mcg/kg ($p < 0.01$). Operating room time was significantly reduced with rFVIIa (122 minutes [SD = 17] for rFVIIa vs. 180 minutes [SD = 16] for usual care, $p < 0.01$). Current evidence is insufficient for comparing harms and benefits. <p>Regarding subpopulations of patients, our findings include:</p>	No Publication identified	No Signal	Not assessed	No Alerts	<p>One of the experts said the conclusion for this question was still valid.</p> <p>However, the expert said the conclusion for this question was NOT still valid. He commented, “No follow-up to the original publication because – in the US at least – there is much less risk of transfusion in this population, and massive transfusion is very unlikely.”</p>	The conclusion is up to date

<ul style="list-style-type: none"> There was inadequate information available to assess the effect of rFVIIa dosage on outcomes other than RBC transfusion requirements. 						
<p>Conclusions</p> <p>Available evidence on off-label rFVIIa use is limited across a wide spectrum of off-label indications. Considering the evidence as a whole, off-label rFVIIa may provide some benefit for certain clinical indications, but this conclusion is largely based on indirect outcomes that have an uncertain relationship to patient survival or functional status. Of the indications we studied, the benefit-to-risk ratio <u>may be more favorable for body trauma than for other indications</u>, because its use may reduce the occurrence of acute respiratory distress syndrome (ARDS); however, the strength of evidence is low for this as well as most other outcomes, which precludes definitive conclusions. <u>Available evidence does not indicate that use of off-label rFVIIa reduces mortality or improves other direct outcomes for the indications we studied</u>. Thromboembolic events are increased by use of rFVIIa in intracranial hemorrhage and adult cardiac surgery. Despite this state of evidence, in-hospital, off-label cases of rFVIIa use have increased in the last decade, particularly for cardiac surgery, trauma, and intracranial hemorrhage.</p>		No Signal	See above	See above	<p>Both of the experts said the conclusion for this question was still valid.</p> <p>The following additional report was recommended: “Lin Y et al. Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia. Cochrane Database Syst Rev. 2011 Feb 16;(2)”</p>	The conclusion is uptodate
CER=comparative effectiveness review; FDA=food and drug administration; vs.: versus; MD: mean difference; NR: Not Reported						

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3. Shojania KG, Sampson M, Ansari MT, et al. How quickly do systematic reviews go out of date? A survival analysis. *Ann Intern Med* 2007 Aug 21;147(4):224-33. [PMID: PM:17638714].
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Appendix A: Search Methodology

All MEDLINE searches were limited to the following journals:

General biomedical – Annals of Internal Medicine, BMJ, JAMA, Lancet, and New England Journal of Medicine

Specialty journals – Trauma-Injury Infection and Critical Care, Neurocritical care, The Annals of Thoracic Surgery, Transplantation, and Stroke

Database: Ovid MEDLINE(R)

Time period covered: 2008 to January 4th, 2012

Main Search

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present> Search Strategy:

-
- 1 exp factor viia/ (3042)
 - 2 ("factor viia" or "factor 7a" or rfviia or fviia).mp. (4135)
 - 3 (novoseven or eptacog* or Niastase or proconvertin or "novo-seven").mp. (515)
 - 4 ec 3 4 21 21.rn. (3042)
 - 5 (((7a or viia) adj5 (factor or rfactor)) or (("factor vii" or "factor 7" or fvii or rfvii or "factor seven") adj5 (active or activated))).mp. (4321)
 - 6 or/1-5 (4675)
 - 7 ("case reports" or editorial or "review").pt. (3377731)
 - 8 animals/ not humans/ (3547231)
 - 9 exp Intracranial Hemorrhages/ (49370)
 - 10 exp Brain/ (873645)
 - 11 exp Skull/ (141291)
 - 12 (intracranial or intracerebral or "basal ganglia" or brain* or "posterior fossa" or cerebral or parenchymal or subdural or subarachnoid or pituitary or epidural).mp. (1327217)
 - 13 or/9-12 (1651479)
 - 14 exp "Wounds and Injuries"/ or (traum* or injur* or wound*).mp. (1127222)
 - 15 exp liver transplantation/ (38059)
 - 16 ((liver* or hepatic) adj3 (transplan* or graft*)).mp. (48142)
 - 17 exp Cardiovascular Diseases/su [Surgery] (218401)
 - 18 exp cardiovascular surgical procedures/ (247450)
 - 19 ((heart* or cardi*) and surg*).mp. (165219)
 - 20 exp Prostatectomy/ (20189)
 - 21 (Prostatectom* or (resect* and prostat*)).mp. (28190)
 - 22 or/15-21 (528775)
 - 23 6 and (13 or 14 or 22) (1360)
 - 24 animals/ not humans/ (3547231)
 - 25 23 not 24 (1280)

26 6 not (7 or 8 or 25) (2038)
 27 ("annals of internal medicine" or bmj or jama or lancet or "new england journal of
 medicine").jn. (324759)
 28 ("annals of thoracic surgery" or "journal of trauma injury infection & critical care" or
 stroke or transplantation or neurocritical care).jn. (78598)
 29 27 or 28 (403357)
 30 26 and 29 (27)
 31 ("20090204" or "20090205" or "20090206" or "20090209" or "20090210" or "20090211"
 or "20090212" or "20090213" or "20090216" or "20090217" or "20090219" or "20090220" or
 "20090223" or "20090224" or "20090225" or "20090226" or "20090227" or 200903* or
 200904* or 200905* or 200906* or 200907* or 200908* or 200909* or 200910* or 200911* or
 200912* or 2010* or 2011* or 2012*).ed. (2627258)
 32 30 and 31 (9)

Factor VIIa - Intracranial Hemorrhage

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid
 MEDLINE(R) <1946 to Present> Search Strategy:

 1 exp factor viia/ (3042)
 2 ("factor viia" or "factor 7a" or rfviia or fviia).mp. (4135)
 3 (novoseven or eptacog* or Niastase or proconvertin or "novo-seven").mp. (515)
 4 ec 3 4 21 21.rn. (3042)
 5 (((7a or viia) adj5 (factor or rfactor)) or (("factor vii" or "factor 7" or fvii or rfvii or "factor
 seven") adj5 (active or activated))).mp. (4321)
 6 or/1-5 (4675)
 7 exp Intracranial Hemorrhages/ (49370)
 8 exp Brain/ (873645)
 9 exp Skull/ (141291)
 10 (intracranial or intracerebral or "basal ganglia" or brain* or "posterior fossa" or cerebral or
 parenchymal or subdural or subarachnoid or pituitary or epidural).mp. (1327217)
 11 or/7-10 (1651479)
 12 6 and 11 (422)
 13 animals/ not humans/ (3547231)
 14 12 not 13 (412)
 15 ("annals of internal medicine" or bmj or jama or lancet or "new england journal of
 medicine").jn. (324759)
 16 ("annals of thoracic surgery" or "journal of trauma injury infection & critical care" or
 stroke or transplantation or neurocritical care).jn. (78598)
 17 15 or 16 (403357)
 18 14 and 17 (45)
 19 ("20090204" or "20090205" or "20090206" or "20090209" or "20090210" or "20090211"
 or "20090212" or "20090213" or "20090216" or "20090217" or "20090219" or "20090220" or
 "20090223" or "20090224" or "20090225" or "20090226" or "20090227" or 200903* or

200904* or 200905* or 200906* or 200907* or 200908* or 200909* or 200910* or 200911* or 200912* or 2010* or 2011* or 2012*).ed. (2627258)
20 18 and 19 (11)

Factor VIIa - Liver Transplantation, etc.

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present> Search Strategy:

1 exp factor viia/ (3042)
2 ("factor viia" or "factor 7a" or rfviia or fviia).mp. (4135)
3 (novoseven or eptacog* or Niastase or proconvertin or "novo-seven").mp. (515)
4 ec 3 4 21 21.rn. (3042)
5 (((7a or viia) adj5 (factor or rfactor)) or (("factor vii" or "factor 7" or fvii or rfvii or "factor seven") adj5 (active or activated))).mp. (4321)
6 or/1-5 (4675)
7 exp liver transplantation/ (38059)
8 ((liver* or hepatic) adj3 (transplan* or graft*)).mp. (48142)
9 exp Cardiovascular Diseases/su [Surgery] (218401)
10 exp cardiovascular surgical procedures/ (247450)
11 ((heart* or cardi*) and surg*).mp. (165219)
12 exp Prostatectomy/ (20189)
13 (Prostatectom* or (resect* and prostat*)).mp. (28190)
14 or/7-13 (528775)
15 6 and 14 (441)
16 animals/ not humans/ (3547231)
17 15 not 16 (433)
18 ("annals of internal medicine" or bmj or jama or lancet or "new england journal of medicine").jn. (324759)
19 ("annals of thoracic surgery" or "journal of trauma injury infection & critical care" or stroke or transplantation or neurocritical care).jn. (78598)
20 18 or 19 (403357)
21 17 and 20 (41)
22 ("20090204" or "20090205" or "20090206" or "20090209" or "20090210" or "20090211" or "20090212" or "20090213" or "20090216" or "20090217" or "20090219" or "20090220" or "20090223" or "20090224" or "20090225" or "20090226" or "20090227" or 200903* or 200904* or 200905* or 200906* or 200907* or 200908* or 200909* or 200910* or 200911* or 200912* or 2010* or 2011* or 2012*).ed. (2627258)
23 21 and 22 (9)

Factor VIIa – Trauma

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present> Search Strategy:

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1  exp factor viia/ (3042)
2  ("factor viia" or "factor 7a" or rfviia or fviia).mp. (4135)
3  (novoseven or eptacog* or Niastase or proconvertin or "novo-seven").mp. (515)
4  ec 3 4 21 21.rn. (3042)
5  (((7a or viia) adj5 (factor or rfactor)) or (("factor vii" or "factor 7" or fvii or rfvii or "factor
seven") adj5 (active or activated))).mp. (4321)
6  or/1-5 (4675)
7  exp "Wounds and Injuries"/ or (traum* or injur* or wound*).mp. (1127222)
8  6 and 7 (772)
9  animals/ not humans/ (3547231)
10  8 not 9 (702)
11  ("annals of internal medicine" or bmj or jama or lancet or "new england journal of
medicine").jn. (324759)
12  ("annals of thoracic surgery" or "journal of trauma injury infection & critical care" or
stroke or transplantation or neurocritical care).jn. (78598)
13  11 or 12 (403357)
14  10 and 13 (54)
15  ("20090204" or "20090205" or "20090206" or "20090209" or "20090210" or "20090211"
or "20090212" or "20090213" or "20090216" or "20090217" or "20090219" or "20090220" or
"20090223" or "20090224" or "20090225" or "20090226" or "20090227" or 200903* or
200904* or 200905* or 200906* or 200907* or 200908* or 200909* or 200910* or 200911* or
200912* or 2010* or 2011* or 2012*).ed. (2627258)
16  14 and 15 (17)

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Factor VIIa - Off-Label – EMBASE

Database: Embase<1980 to 2011 Week 52>

Search Strategy:

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1  exp blood clotting factor 7a/ (2265)
2  ("factor viia" or "factor 7a" or rfviia or fviia).mp. (7376)
3  (novoseven or eptacog* or Niastase or proconvertin or "novo-seven").mp. (1835)
4  (("factor vii" or "factor 7" or fvii or rfvii or "factor seven") adj5 (active or activated)).mp.
(1897)
5  or/1-4 (7840)
6  letter.pt. (751128)
7  (animal/ or nonhuman/) not human/ (4320497)
8  exp brain hemorrhage/ or exp brain/ or exp skull/ (1026153)
9  (intracranial or intracerebral or "basal ganglia" or brain* or "posterior fossa" or cerebral or
parenchymal or subdural or subarachnoid or pituitary or epidural).mp. (1480090)
10  8 or 9 (1803455)
11  exp stroke/ or cerebrovascular accident/ (140442)
12  (CVA or stroke or apoplexy or brain vascular accident* or cerebrovascular accident*).mp.
(211200)
13  11 or 12 (211200)

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- 14 exp bleeding/ (445682)
- 15 (hemorrhage* or bleed).mp. (213077)
- 16 14 or 15 (474764)
- 17 13 and 16 (30006)
- 18 10 or 17 (1812945)
- 19 exp liver transplantation/ (57515)
- 20 ((liver* or hepatic) adj5 (transplan* or graft*)).mp. (73682)
- 21 exp cardiovascular surgery/ (402803)
- 22 exp cardiovascular disease/su [Surgery] (263660)
- 23 ((heart* or cardi*) and (surg* or presurg* or postsurg* or perioperat* or operation* or operative or perioperat* or preoperat* or postoperat* or resect*)).tw. (190075)
- 24 exp prostatectomy/ (28322)
- 25 (prostatectom* or (prostat* and (surg* or presurg* or postsurg* or perioperat* or operation* or operative or perioperat* or preoperat* or postoperat* or resect*))).mp. (52478)
- 26 or/19-25 (725256)
- 27 exp injury/ (1218709)
- 28 (traum* or injur* or wound*).mp. (1150465)
- 29 27 or 28 (1525514)
- 30 5 and (18 or 26 or 29) (3098)
- 31 (animal/ or nonhuman/) not human/ (4320497)
- 32 30 not 31 (2974)
- 33 5 not (6 or 7 or 32) (4131)
- 34 ("annals of internal medicine" or bmj or bmj clinical research ed or "jama journal of the american medical association" or "jama the journal of the american medical association" or lancet or "new england journal of medicine").jn. (240293)
- 35 ("journal of trauma" or "annals of thoracic surgery" or transplantation or stroke or "stroke a journal of cerebral circulation" or neurocritical care).jn. (68292)
- 36 34 or 35 (308585)
- 37 33 and 36 (30)
- 38 (2009* or 2010* or 2011*).em. (3412617)
- 39 37 and 38 (7)

Factor VIIa - Intracranial Hemorrhage - EMBASE

Database: Embase<1980 to 2011 Week 52>

Search Strategy:

- 1 exp blood clotting factor 7a/ (2265)
- 2 ("factor viia" or "factor 7a" or rfviia or fviia).mp. (7376)
- 3 (novoseven or eptacog* or Niastase or proconvertin or "novo-seven").mp. (1835)
- 4 (("factor vii" or "factor 7" or fvii or rfvii or "factor seven") adj5 (active or activated)).mp. (1897)
- 5 or/1-4 (7840)
- 6 exp brain hemorrhage/ (66908)
- 7 exp brain/ (851090)

- 8 exp skull/ (131079)
- 9 (intracranial or intracerebral or "basal ganglia" or brain* or "posterior fossa" or cerebral or parenchymal or subdural or subarachnoid or pituitary or epidural).mp. (1480090)
- 10 or/6-9 (1803455)
- 11 exp stroke/ (110200)
- 12 cerebrovascular accident/ (37456)
- 13 (CVA or stroke or apoplexy or brain vascular accident* or cerebrovascular accident*).mp. (211200)
- 14 or/11-13 (211200)
- 15 exp bleeding/ (445682)
- 16 (hemorrhage* or bleed).mp. (213077)
- 17 15 or 16 (474764)
- 18 14 and 17 (30006)
- 19 10 or 18 (1812945)
- 20 5 and 19 (1274)
- 21 (animal/ or nonhuman/) not human/ (4320497)
- 22 20 not 21 (1259)
- 23 ("annals of internal medicine" or bmj or bmj clinical research ed or "jama journal of the american medical association" or "jama the journal of the american medical association" or lancet or "new england journal of medicine").jn. (240293)
- 24 ("journal of trauma" or "annals of thoracic surgery" or transplantation or stroke or "stroke a journal of cerebral circulation" or neurocritical care).jn. (68292)
- 25 23 or 24 (308585)
- 26 22 and 25 (87)
- 27 (2009* or 2010* or 2011*).em. (3412617)
- 28 26 and 27 (40)

Factor VIIa - Liver Transplantation, etc. – EMBASE

Database: Embase<1980 to 2011 Week 52>

Search Strategy:

- 1 exp blood clotting factor 7a/ (2265)
- 2 ("factor viia" or "factor 7a" or rfviia or fviia).mp. (7376)
- 3 (novoseven or eptacog* or Niasase or proconvertin or "novo-seven").mp. (1835)
- 4 (("factor vii" or "factor 7" or fvii or rfvii or "factor seven") adj5 (active or activated)).mp. (1897)
- 5 or/1-4 (7840)
- 6 exp liver transplantation/ (57515)
- 7 ((liver* or hepatic) adj5 (transplan* or graft*)).mp. (73682)
- 8 exp cardiovascular surgery/ (402803)
- 9 exp cardiovascular disease/su [Surgery] (263660)
- 10 ((heart* or cardi*) and (surg* or presurg* or postsurg* or perioperat* or operation* or operative or perioperat* or preoperat* or postoperat* or resect*)).tw. (190075)
- 11 exp prostatectomy/ (28322)

- 12 (prostatectom* or (prostat* and (surg* or presurg* or postsurg* or perioperat* or operation* or operative or perioperat* or preoperat* or postoperat* or resect*))).mp. (52478)
- 13 or/6-12 (725256)
- 14 5 and 13 (1207)
- 15 (animal/ or nonhuman/) not human/ (4320497)
- 16 14 not 15 (1183)
- 17 ("annals of internal medicine" or bmj or bmj clinical research ed or "jama journal of the american medical association" or "jama the journal of the american medical association" or lancet or "new england journal of medicine").jn. (240293)
- 18 ("journal of trauma" or "annals of thoracic surgery" or transplantation or stroke or "stroke a journal of cerebral circulation" or neurocritical care).jn. (68292)
- 19 17 or 18 (308585)
- 20 16 and 19 (78)
- 21 (2009* or 2010* or 2011*).em. (3412617)
- 22 20 and 21 (29)

Factor VIIa - Trauma – EMBASE

Database: Embase<1980 to 2011 Week 52>

Search Strategy:

-
- 1 exp blood clotting factor 7a/ (2265)
 - 2 ("factor viia" or "factor 7a" or rfviia or fviia).mp. (7376)
 - 3 (novoseven or eptacog* or Niastase or proconvertin or "novo-seven").mp. (1835)
 - 4 (("factor vii" or "factor 7" or fvii or rfvii or "factor seven") adj5 (active or activated)).mp. (1897)
 - 5 or/1-4 (7840)
 - 6 exp injury/ (1218709)
 - 7 (traum* or injur* or wound*).mp. (1150465)
 - 8 or/6-7 (1525514)
 - 9 5 and 8 (1673)
 - 10 (animal/ or nonhuman/) not human/ (4320497)
 - 11 9 not 10 (1568)
 - 12 ("annals of internal medicine" or bmj or bmj clinical research ed or "jama journal of the american medical association" or "jama the journal of the american medical association" or lancet or "new england journal of medicine").jn. (240293)
 - 13 ("journal of trauma" or "annals of thoracic surgery" or transplantation or stroke or "stroke a journal of cerebral circulation" or neurocritical care).jn. (68292)
 - 14 or/12-13 (308585)
 - 15 11 and 14 (47)
 - 16 (2009* or 2010* or 2011*).em. (3412617)
 - 17 15 and 16 (24)

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to December 2011>, EBM Reviews - ACP Journal Club <1991 to December 2011>, EBM Reviews - Database of Abstracts of Reviews of Effects <4th Quarter 2011>, EBM Reviews - Cochrane Central Register of Controlled Trials <4th Quarter 2011>, EBM Reviews - Cochrane Methodology Register <4th Quarter 2011>, EBM Reviews - Health Technology Assessment <4th Quarter 2011>, EBM Reviews - NHS Economic Evaluation Database <4th Quarter 2011> Search Strategy:

-
- 1 ("factor viia" or "factor 7a" or rfviia or fviia or novoseven or eptacog* or Niastase or proconvertin or "novo-seven").mp. (295)
 - 2 ((7a or viia) adj5 (factor or rfactor)).mp. (233)
 - 3 (("factor vii" or "factor 7" or fvii or rfvii or "factor seven") adj5 (active or activated)).mp. (193)
 - 4 or/1-3 (348)
 - 5 limit 4 to yr="2009 -Current" [Limit not valid in DARE; records were retained] (75)
 - 6 from 5 keep 14,28,30,36,40,42-43 (7)
 - 7 from 5 keep 75 (1)
 - 8 6 or 7 (8)

Factor VIIa

BIOSIS - 2011 Jan 4

(Note: *Annals of Thoracic Surgery and Neurocritical Care* not included in BIOSIS)

Search Strategy:

10

[23](#)

#6 AND #9

Databases=BIOSIS Previews Timespan=2009-2012

Lemmatization=On

9

[9,686](#)

#7 OR #8

Databases=BIOSIS Previews Timespan=2009-2012

Lemmatization=On

8

[4,811](#)

SO=(JOURNAL OF TRAUMA INJURY INFECTION "AND" CRITICAL CARE OR TRANSPLANTATION HAGERSTOWN OR STROKE)

Databases=BIOSIS Previews Timespan=2009-2012

Lemmatization=On

7

[4,875](#)

SO=(ANNALS OF INTERNAL MEDICINE OR BMJ OR JAMA JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION OR LANCET NORTH AMERICAN EDITION OR NEW ENGLAND JOURNAL OF MEDICINE)

Databases=BIOSIS Previews Timespan=2009-2012

Lemmatization=On

6

[516](#)

#5

Databases=BIOSIS Previews Timespan=2009-2012

Lemmatization=On

5

[3,747](#)

#3 NOT #4

Databases=BIOSIS Previews Timespan=All Years

Lemmatization=

4

[5,262,057](#)

TA=((Animals) NOT (Humans))

Databases=BIOSIS Previews Timespan=All Years

Lemmatization=On

3

[4,284](#)

#1 NOT #2

Databases=BIOSIS Previews Timespan=All Years

Lemmatization=On

2

[114,516](#)

(DT=letter) AND Document Types=(Letter)

Databases=BIOSIS Previews Timespan=All Years

Lemmatization=On

1

[4,399](#)

Topic=("factor viia" or "factor 7a" OR rfvia OR fvia OR novoseven or eptacog* OR Niastase OR proconvertin OR "novo-seven") OR Topic=((7a or viia) NEAR/5 (factor OR rfactor)) OR Topic=((("factor vii" OR "factor 7" OR fvii OR rfvii OR "factor seven") NEAR/5 (active OR activated))

Databases=BIOSIS Previews Timespan=All Years

Lemmatization=On

Appendix B: Updating Signals

Qualitative signals*

Potentially invalidating change in evidence

This category of signals (A1-A3) specifies findings from a pivotal trial**, meta-analysis (with at least one new trial), practice guideline (from major specialty organization or published in peer-reviewed journal), or recent textbook (e.g., *UpToDate*):

- Opposing findings (e.g., effective vs. ineffective) – **A1**
- Substantial harm (e.g., the risk of harm outweighs the benefits) – **A2**
- A superior new treatment (e.g., new treatment that is significantly superior to the one assessed in the original CER) – **A3**

Major change in evidence

This category of signals (A4-A7) refers to situations in which there is a clear potential for the new evidence to affect the clinical decision making. These signals, except for one (A7), specify findings from a pivotal trial, meta-analysis (with at least one new trial), practice guideline (from major specialty organization or published in peer-reviewed journal), or recent textbook (e.g., *UpToDate*):

- Important changes in effectiveness short of “opposing findings” – **A4**
- Clinically important expansion of treatment (e.g., to new subgroups of subjects) – **A5**
- Clinically important caveat – **A6**
- Opposing findings from meta-analysis (in relation to a meta-analysis in the original CER) or non-pivotal trial – **A7**

* Please, see Shojania et al. 2007 for further definitions and details

**A pivotal trial is defined as: 1) a trial published in top 5 general medical journals such as: Lancet, JAMA, Annals of Intern Med, BMJ, and NEJM. Or 2) a trial not published in the above top 5 journals but have a sample size of at least triple the size of the previous largest trial in the original CER.

Appendix B: Updating Signals (Continued)

Quantitative signals (B1-B2)*

Change in statistical significance (B1)

Refers to a situation in which a statistically significant result in the original CER is now NOT statistically significant or vice versa- that is a previously non-significant result become statistically significant. For the ‘borderline’ changes in statistical significance, at least one of the reports (the original CER or new updated meta-analysis) must have a p-value outside the range of border line (0.04 to 0.06) to be considered as a quantitative signal for updating.

Change in effect size of at least 50% (B2)

Refers to a situation in which the new result indicates a relative change in effect size of at least 50%. For example, if relative risk reduction (RRR) new / RRR old ≤ 0.5 or RRR new / RRR old ≥ 1.5 . Thus, if the original review has found RR=0.70 for mortality, this implies RRR of 0.3. If the updated meta-analytic result for mortality were 0.90, then the updated RRR would be 0.10, which is less than 50% of the previous RRR. In other words the reduction in the risk of death has moved from 30% to 10%. The same criterion applied for odds ratios (e.g., if previous OR=0.70 and updated result were OR=0.90, then the new reduction in odds of death (0.10) would be less 50% of the magnitude of the previous reduction in odds (0.30). For risk differences and weighted mean differences, we applied the criterion directly to the previous and updated results (e.g., RD new / RD old ≤ 0.5 or RD new / RD old ≥ 1.5).

* Please, see Shojania et al. 2007 for further definitions and details

Appendix C: Evidence Table (Factor VIIa)

Author year Study name (if applicable)	Study design	participants	Intervention groups (n; dose)	Treatment duration	Primary outcome	Findings
Key Question 1. Indications, Populations, and Characteristics of Comparative Studies of Off-Label rFVIIa Use						
Robinson MT, 2010 ⁹	Non RCT	101 pts with (54% had Intracranial heamorrhage and 30% subdural hematomas); Mean age: 76 yrs; Male: 48.6%	rFVIIa, mean total dose: 51.7 ±28.99 µg/kg (n=101)	2002- 2009	Thromboembolic events	<u>RFVIIa</u> Rate of thromboembolic complications: 5% (all venous)
Christensen MC, 2010 ⁸	RCT	560 pts with trauma; Mean age: 38±15; Male: 79%	rFVIIa, dose:NR (n=NR) vs. placebo (n=NR)	Three years	Clinical outcomes	<u>USA vs. other countries</u> Between countries differences in Mortality (Admission -24 hrs): OR, 95%CI <u>Australia:</u> 0.16; 0.01,4.33 <u>Brazil:</u> 6.48; 0.00–10028.35 <u>Canada:</u> 1.02; 0.01–133.45 <u>Switzerland:</u> 0.53; 0.00–190.35 <u>Czech Republic:</u> 10.97; 0.08–1600.40 <u>Germany:</u> 0.01; 0.00–10.27 <u>Spain:</u> 0.06; 0.00–4.80 <u>Italy:</u> 0.09; 0.00–219.16 <u>Singapore:</u> 23.92; 0.22–2652.23 <u>South Africa:</u> 1.61; 0.00–664.78 Predictors of Mortality: OR, 95% CI <u>RBC≥10 units Admission–24 hr:</u> 6.74; 1.14, 32..30; p<0.05 In admission -24 hrs <u>RBC≥10 units Admission–24 hr:</u> 4.24; 1.97,9.12; p<0.01 In admission- 90days <u>Chest injury AIS score 4:</u> 4.51; 3.31,24.81;

Author year Study name (if applicable)	Study design	participants	Intervention groups (n; dose)	Treatment duration	Primary outcome	Findings
						<p>p<0.01 in Admission- 24 hrs <u>Male:</u> 4.07; (1.27, 13.02; p<0.05 <u>Age ≥ 60 yrs:</u> 4.00; 1.61, 9.92; p<0.01</p>
McMullin NR, 2010 ¹³	RCT	169 pts with trauma; Mean age: 31.5 yrs; Male: 88%	rFVIIa, dose:NR (n=86) vs. placebo (n=83)	NR	Clinical outcomes	<p><u>rFVIIa [1-h PT ≥18 seconds vs. In >18 seconds:</u></p> <p>24 hr- Mortality with 1-hr PT time: n(%) 6 (60) vs. 4 (11); p<0.001 30 day Mortality: n(%) 6 (60) vs. 8 (11); p=0.001 Massive Transfusion (≥20 units of RBC within 48 hr of admission): n(%) 4 (44) vs. 8 (11); p=0.022</p> <p><u>Placebo [1-h PT ≥18 seconds vs. In >18 seconds:</u></p> <p>24 hr- Mortality with 1-hr PT time: n(%) 4 (11) vs. 1 (2); p<0.174 30 day Mortality: n(%) 11 (30) vs. 6 (14); p=0.102 Massive Transfusion (≥20 units of RBC within 48 hr of admission): n(%) 14 (39) vs. 3 (7); p<0.001</p>
Witmer CM, 2011 ¹⁸	Non RCT	4942 children (3655 with off label admissions, and 1287 with on label admissions for rFVIIa); Age:0-18 yrs; Male: 67.4%	rFVIIa; dose:NR (n=4942)	2000-2007	Thrombosis	<p><u>rFVIIa off-label vs. on label</u></p> <p>Usage in years 2000-2007: 1- A 10-fold increase in the annual rate of off-label admission from 2000-2007, from 2 to 20.8 per 10,000 hospital admissions (p<0.001). 2- A 2-fold increase in the label use from 2.1 to 4.3 per 10,000 admissions (p<0.001) Admitting service for Off-label: 1- Hematology/oncology: 16.8%</p>

Author year Study name (if applicable)	Study design	participants	Intervention groups (n; dose)	Treatment duration	Primary outcome	Findings
						2- Critical care: 16.1% 3- Cardiology: 10.3% 4- Cardiovascular/thoracic surger: 10.2% 5- Combined cardiovascular surgery and cardiology: 20.5%
Stanworth SJ, 2011 ¹⁶	Review of RCTs	3500 patients either at risk of major bleeding, or who have uncontrolled bleeding; Mean Age: all ages; Male: NR.	rFVIIa 5 µg/kg- 360 µg/kg (n=NR) vs. placebo or another dose of rFVIIa (n=NR)		Mortality, bleeding, RBC requirement, adverse effects	<u>rFVIIa vs. placebo or another dose of rFVIIa:</u> <u>Prophylactic use of rFVIIa:</u> Mortality: RR: 1.06; 95%CI: 0.50, 2.24 RBC requirement: WMD: 243ml; 95%CI: -393, -92 Thromboembolic events: RR: 1.32; 95% CI: 0.84, 2.06 <u>Therapeutic use of rFVIIa</u> Mortality: RR: 0.89; 95% CI: 0.77, 1.03 Thromboembolic events: RR: 1.21; 95% CI: 0.93, 1.58
All of the seven following publications that are included in the following questions.						
Key question # 2: Use of rFVIIa for Selected Indications in Patient With/Undergoing Intracranial Hemorrhage						
Levi M, 2010 ⁵	RCT	1397 pts with spontaneous central nervous system bleeding; Mean age:65yrs; Male:NR	rFVIIa 80 - >120 µg/kg; (n=974) vs. placebo (n=423)	NR	Thromboembolic events	<u>rFVIIa vs. placebo</u> Atrial Thromboembolic Event: OR: 1.67; 95% CI: 1.03, 2.69; p= 0.04
Diringer MN, 2009 ¹⁰	RCT	841 pts with intracerebral hemorrhage; Mean age: 65±14 yrs; Male:62%	rFVIIa 20 or 80 µg/kg (n=573) vs. placebo (n=268)	NR	Death, TE	<u>rFVIIa (20 µg/kg), 80 µg/kg vs. placebo</u> Atrial Thromboembolic Event: n(%) 47 (26%) , 82 (46%) vs. 49 (27%); p=0.04 Venous Thromboembolic Event:

Author year Study name (if applicable)	Study design	participants	Intervention groups (n; dose)	Treatment duration	Primary outcome	Findings
						<p>Similar across groups</p> <p>Arterial TEs were associated with: <u>Receiving 80 µg/kg rFVIIa:</u> OR=2.14; 95% CI: 1.09, 4.41; <i>P</i>=0.031 (compared to 20 µg/kg and placebo) <u>Signs of cardiac or cerebral ischemia at presentation:</u> OR=4.19; 95% CI: 1.03, 1.27; <i>P</i>=0.010) <u>Age:</u> OR=1.14/5 years; <i>P</i>=0.0123 <u>Prior use of antiplatelet agents:</u> OR=1.83; 95% CI: 1.04, 3.20; <i>P</i>=0.035</p> <p>Logistic regression analysis showed that the risk of having an arterial thrombotic event was significantly increased in the 80µg/kg rFVIIa dose group compared with 20µg/kg or placebo.</p>
Key question # 3a: Use of rFVIIa for Selected Indications in Patient With/Undergoing Massive Bleeding from Trauma (Body Trauma)						
Dutton RP, 2011 ¹¹	RCT	560 pts with trauma; Mean age: NR; Male:NR	rFVIIa, dose:NR (n=270) vs. placebo (n=290)	NR	30-day Mortality, organ system failure at 30 days, volume of red blood cells transfused, and incidence of major complications.	<p><u>FVIIa vs. placebo</u></p> <p>30- day Mortality: n(%) 32 (12.2) vs. 31 (11.1); <i>p</i>= 0.61</p> <p>All Adverse Events: n(%) 240 (88.9) vs. 256 (88.3); <i>p</i>= 0.82</p> <p>Adverse Events Related to thromboembolic events as Reported by Site Investigators: n(%) <u>Atrial:</u> 16 (5.9) vs. 12 (4.1); <i>p</i>= 0.33 <u>Venous:</u> 25 (9.3) vs. 26 (9.0); <i>p</i>= 0.90 Confirmed thromboembolic events: 47 (100.0) vs. 40 (100.0); <i>p</i>=NR Acute respiratory distress syndrome: n(%) 8 (3.0) vs. 21 (7.2); <i>p</i>= 0.02</p>
Wade CE,2010	Non	2050 pts with combat	rFVIIa, dose:NR (n=506)	Five years	Casualties	<u>rFVIIa vs. No rFVIIa</u>

Author year Study name (if applicable)	Study design	participants	Intervention groups (n; dose)	Treatment duration	Primary outcome	Findings
¹²	RCT	causalities; Mean age: 24yrs; Male: NR	vs. placebo (n=1544)		outcomes	Mortality Rate (propensity matched): % 19.9 vs. 14.3; p=NS Multivariate Regression of Variables Associated With Overall Mortality: <u>RFVIIa use:</u> OR: 1.672, 95% CI: 1.079, 2.593; p=0.022 Complications rate: 21% vs. 21%; p=NS RBC Use: [value(range)] 10 (6–16) vs. 10(4–17); p<NS
Hauser CJ, 2010 ⁷	RCT	573 pts with (481 blunt and 92 penetrating) trauma; Mean age: 35 yrs; Male: 74%	rFVIIa (200 µg/kg at 0 hour, 100µg/kg at 1 hour and 3 hours) (n= 264) vs. placebo (n=287)	Three years	30-day mortality	<u>rFVIIa vs. placebo</u> Blunt Trauma: n(%) 30-d mortality: 24 (11.0) vs. 26 (10.7); p= 0.93 Durable morbidity: 19 (8.7) vs. 23 (9.5); p= 0.75 Penetrating Trauma: n(%) 30-d mortality: 8 (18.2) vs. 5 (13.2); p= 0.40 Durable morbidity: 1 (2.3) vs. 0; p= 1.00 RBC Requirement <u>Blunt Trauma: (mean±SD)</u> <u>24 hours:</u> 6.9±10.4 vs. 8.1 ± 10.9; p= 0.04 <u>48 hours:</u> 7.8 ± 10.6 vs. 9.1±11.3; p= 0.04 <u>Penetrating Trauma</u> <u>24 hours:</u> 4.5±7.3 vs. 6.2±6.5; p= 0.11 <u>48 hours:</u> 5.0±7.4 vs. 6.8 ± 6.9; p= 0.11
Morse BC, 2011 ¹⁹	Non RCT	117 pts with trauma undergoing massive transfusion; Mean age: 34±1.95; Male: 80%	rFVIIa 4mg (n=39) vs. No rFVIIa (n=78)	3 years	Mortality	<u>rFVIIa vs. No rFVIIa</u> 24-hour Mortality in patients required: ≥30 unites of packed RBC: 26% vs. 64%; p=0.02

Author year Study name (if applicable)	Study design	participants	Intervention groups (n; dose)	Treatment duration	Primary outcome	Findings
						<p>21-30 unites of packed RBC: 44% vs. 47%; p=0.83 ≤20 unites of packed RBC: 25% vs. 24%; p=0.95</p> <p>Mean Transfusion Requirement (packed RBC): 6-hour Transfusion: 35.6±2.6 vs. 25.6±0.7; p=0.001 24-hour Transfusion: 38.6±2.9 vs. 28.0±1.0; p=0.001</p>
Levi M, 2010 ⁵	RCT	837 pts with Trauma; Mean age: 50.9 yrs; Male:NR	rFVIIa 80 - >120 µg/kg; (n=61) vs. placebo (n=36)	NR	Thromboembolic events	<p><u>rFVIIa vs. placebo</u></p> <p>Atrial Thromboembolic Event: OR: 1.39; 95% CI: 0.69, 2.77 ; p=0.36</p>
Key question # 3b: Use of rFVIIa for Selected Indications in Patient With/Undergoing Massive Bleeding from Trauma (Brain Trauma) i.e., Traumatic Brain Injury [TBI])						
Levi M, 2010 ⁵	RCT	97 pts with Traumatic brain injury; Mean age: 50.9 yrs; Male:NR	rFVIIa 80 - >120 µg/kg; (n=61) vs. placebo (n=36)	NR	Thromboembolic events	<p><u>rFVIIa vs. placebo</u></p> <p>Atrial Thromboembolic Event: No./total no. (%) 2/61(3.3) vs. 1/36 (2.8)</p>
Brown CV, 2010 ¹⁴	Non RCT	28 pts with blunt trauma with traumatic brain injury who presented coagulopathic; Mean age: 50yrs; Male 79%	rFVIIa 1.2mg (n=14) vs. no- rFVIIa (n=14)	Two years	Mortality and others	<p><u>rFVIIa vs. no rFVIIa</u></p> <p>Mortality: n(%) 7*(50) vs. 4(29); p=0.22 * though four deaths were secondary to withdrawal of care according to patient and family wishes Thromboembolic complication:</p>

Author year Study name (if applicable)	Study design	participants	Intervention groups (n; dose)	Treatment duration	Primary outcome	Findings
						0 vs. 0 Packed red blood cells usage [(value (range))]: 4 (1–5) vs. 14 (10–17); p= 0.001
Key question # 4a: Use of rFVIIa for Selected Indications in Patient With/Undergoing Liver Transplantation						
Chavez-Tapia NC, 2011 ¹⁵	Meta analysis of RCTs	671 pts with liver resection and liver transplantation; Mean age: NR; Male: NR	rFVIIa 20-120 µg/kg (n=NR) vs. placebo (n= NR)		Efficacy and safety of rFVIIa in reducing transfusion requirement , Haemostatic effect	<u>rFVIIa vs. Placebo</u> Mortality: OR; 95% CI 0.96; 0.35, 2.62 red blood cells units: MD; 95% CI 0.32; -0.08,0.72 Adverse events: OR; 95% CI 1.55; 0.97, 2.49
Key question # 4b.i. Use of rFVIIa for Selected Indications in Patient With/Undergoing Cardiac Surgery (Adult Cardiac Surgery)						
Levi M, 2010 ⁵	RCT	267 pts with Cardiac surgery; Mean age: 45.4 yrs; Male:NR	rFVIIa 80 - 120 µg/kg; (n=153) vs. placebo (n=114)	NR	Thromboembolic events	<u>rFVIIa vs. placebo</u> Atrial Thromboembolic Event: OR: 1.59; 95% CI: 0.47, 5.34; p= 0.45
Uber WE, 2011 ¹⁷	Non RCT	24 pts undergoing cardiovascular surgery; Median age: 62.5yrs, Male: 95%	rFVIIa, average dose 89.9±7.1µg/kg per dose (n=12) vs. reoperation for refractory bleeding after surgery	December 2033- September 2007	Operation Room time, ventilator time, ICU and hospital LOS, and survival	<u>rFVIIa vs. reoperation for refractory bleeding after surgery:</u> <u>Median Operating room time:</u> Values:NR ;p<0.05 <u>Conclusion:</u> administration of rFVIIa in ICU seems comparable with reoperation for refractory bleeding after complex cardiovascular surgical procedures and might represent an alternative to reoperation in selected patients.
Key question # 4b:ii . Use of rFVIIa for Selected Indications in Patient With/Undergoing Cardiac Surgery (Pediatric Cardiac Surgery)						
Karsies TJ, 2010 ⁶	Non RCT	25 pts with congenital heart disease matched with 50 controls; Mean Age: 56±9 months;	rFVIIa mean dose: 70 mcg/kg vs. controls; Mean Age: 56 ±9 months; Male: 57%	January 1, 1999 to December 31, 2005	Thromboembolic safety profile, mortality	<u>rFVIIa vs. controls</u> Rate of thrombosis 8% vs 4%;p=NR Mortality:

Author year Study name (if applicable)	Study design	participants	Intervention groups (n; dose)	Treatment duration	Primary outcome	Findings
		Male: 57%				No difference Median total transfusion volume: 93.2 mL/kg vs. 108.3 mL/kg; $p = 0.225$
Key Question 4c. Use of rFVIIa for Selected Indications in Patient With/Undergoing Prostatectomy						
No publication was identified.						
Abbreviations: yrs: years old; NR: Not reported; RCT: Randomized Clinical Trial; vs: versus; no: number; %: percent; pts: patients; AIS: abbreviated injury scale; PT: Prothrombin Time; NS: Not significant; RBC: Red Blood Cell; SD: Standard Deviation ;N: total number;						

Appendix D: Questionnaire Matrix

Comparative Effectiveness of In-Hospital Use of Recombinant Factor VIIa for Off-Label Indications vs. Usual Care

AHRQ Publication No. 10-EHC030-EF May 2010

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Responses from expert # 1

Conclusions from CER (executive summary)	Is the conclusion(s) in this CER still valid? (Yes/No/Don't know)	Are you aware of any new evidence that is sufficient to invalidate the finding(s) in CER? (Yes/No/Don't know) If yes, please provide references	Comments
Key Question 1. Indications, Populations, and Characteristics of Comparative Studies of Off-Label rFVIIa Use			
Signal detection was not applicable for this question.			
Key Question 2. Use of rFVIIa for Selected Indications in Patient With/Undergoing Intracranial Hemorrhage			
For intracranial hemorrhage, because there were indications in the literature regarding a possible dose–response relationship between rFVIIa and certain outcomes (e.g., thromboembolic events) and multiple doses of rFVIIa were analyzed in each RCT, we chose <i>a priori</i> to analyze the data according to low-, medium-, and high-dose rFVIIa groups, defined as less than or equal to 40 µg/kg, greater than 40 but less 120 µg/kg, and at least 120 µg/kg, respectively. There were ES-9 four RCTs (two <i>good</i> quality, two <i>fair</i> quality) and one small comparative observational studies (<i>fair</i> quality) that assessed 968 patients who received rFVIIa. The RCTs evaluated patients who were not on oral anticoagulation therapy (OAT) and had intracerebral hemorrhage (ICH), whereas the observational study examined patients on OAT who could have experienced ICH or other forms of intracranial hemorrhage (e.g., subdural bleeding). These studies yielded moderate strength of evidence with good applicability for treatment use in the population targeted	Yes. Only other articles that I am aware are: Annamaria Nosari et al.. (2012) Cerebral hemorrhage treated with NovoSeven in acute promyelocytic leukemia. <i>Leukemia & Lymphoma</i> 53:1, 160-161	No	

<p>by the RCTs—patients with intracerebral hemorrhage who were not on anticoagulation therapy. In all cases where meta-analyses were performed, the results of the risk difference and arcsine metrics were consistent. The risk difference summary statistics are reported below. Regarding the benefits and harms of rFVIIa, our findings include: (Figure C).</p> <ul style="list-style-type: none"> • There was no effect of rFVIIa on mortality (risk difference: low-dose group: 0.031 (95 percent CI -0.086 to 0.024), medium-dose group: 0.020 (95 percent CI -0.076 to 0.036), high-dose group: 0.027 (95 percent CI -0.121 to 0.068); <i>p</i> value of the <i>Q</i> statistic for all risk differences is 0.248) (also see Figure C: each circle represents a study; larger circles correspond to larger studies; shaded circles represent studies on treatment use of rFVIIa, and white circles represent studies on prophylactic use of rFVIIa). rFVIIa use also did not reduce the rate of poor functional outcome as measured on the modified Rankin Scale (risk difference: low-dose group: 0.024 (95 percent CI -0.093 to 0.045), medium-dose group: 0.029 (95 percent CI -0.099 to 0.041), high-dose group: 0.040 (95 percent CI -0.154 to 0.075); <i>p</i> value of the <i>Q</i> statistic for all risk differences is 0.088). • There was an increased rate of arterial thromboembolic events with rFVIIa use vs. usual care for the medium- and high-dose groups (risk difference: low-dose group: 0.025 (95 percent CI -0.004 to 0.053), medium-dose group: 0.035 (95 percent CI 0.008 to 0.062), high-dose group: 0.063 (95 percent CI 0.011 to 0.063); <i>p</i> value of the <i>Q</i> statistic for all risk differences is 0.277) (see Figure D). • rFVIIa use significantly decreased the percent relative hematoma expansion (standardized mean difference: low-dose group: 0.146 (95 percent CI -0.291 to -0.001), medium-dose group: 0.240 (95 percent CI -0.385 to 0.095), high-dose group: 0.334 			
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<p>(95 percent CI -0.579 to -0.090); p value of the Q statistic for all risk differences is 0.840).</p> <ul style="list-style-type: none"> • In summary, current evidence of moderate strength suggests that neither benefits nor harms substantially exceed each other for rFVIIa use in the ICH subgroup of intracranial hemorrhage. <p>Regarding subpopulations of patients, our findings include:</p> <ul style="list-style-type: none"> • Earlier administration of rFVIIa for ICH may increase benefits, but this finding may be confounded by earlier CT scanning among these patients. • There may be greater benefits in younger patients with smaller initial hematoma size. • There was no evidence of a dose effect for any endpoint. • Evolution of intracranial hemorrhage management may reduce the size of the population in which there is a potential benefit of rFVIIa. • There were insufficient studies to assess the impact of rFVIIa on patients taking oral anticoagulation therapy 			
Key Question 3a. Use of rFVIIa for Selected Indications in Patient With/Undergoing Massive Bleeding from Trauma (Body Trauma)			
<p>There were two RCTs (both published in a single paper and of <i>fair</i> quality) and three comparative observational studies (all <i>fair</i> quality) with 267 patients who received rFVIIa. This yielded low strength of evidence with fair applicability for treatment use in the population targeted—patients with blunt or penetrating trauma who were not censored for early in-hospital death (defined as 24 hours or 48 hours depending on the study). Regarding the benefits and harms of rFVIIa, our findings include:</p> <ul style="list-style-type: none"> • There was no effect of rFVIIa on mortality (Figure C) or thromboembolism (Figure D) relative to usual care. • For acute respiratory distress syndrome, the blunt trauma RCT demonstrated a significant reduction with rFVIIa use vs. usual care, while the remaining two studies that evaluated this outcome (the 	<p>Yes. Only other articles that I am aware are:</p> <p>Morse BC et al. The effects of protocolized use of recombinant factor VIIa within a massive transfusion protocol in a civilian level I trauma center. Am Surg. 2011 Aug;77(8):1043-9.</p> <p>Dutton RP et al. Recombinant activated factor VII safety in trauma patients: results from the CONTROL trial. J Trauma. 2011</p>	<p>No</p>	<p>May be able to have info on safety based on more recently published data from the CONTROL trial</p>

<p>penetrating trauma RCT and one observational study) showed a nonsignificant trend in the same direction.</p> <ul style="list-style-type: none"> There was conflicting evidence regarding RBC transfusion requirements. These were significantly decreased among patients receiving rFVIIa vs. usual care in one RCT ($p = 0.02$) and nonsignificantly decreased in the other RCT ($p = 0.10$). In contrast, the one observational study that independently measured this found a significant increase in RBC transfusion requirements ($p = 0.02$). Overall, current evidence of low strength suggests the potential for benefit and little evidence of increased harm. <p>Regarding subpopulations of patients, our findings include:</p> <ul style="list-style-type: none"> Patients with blunt trauma may experience greater benefits than those with penetrating trauma. Greater benefits are also possible in patients with higher baseline pH, shorter time to administration, and higher platelet counts. There was inadequate information available to assess the effect of rFVIIa dosage. 	Jul;71(1):12-9.		
Key Question 3b. Use of rFVIIa for Selected Indications in Patient With/Undergoing Massive Bleeding from Trauma (Brain Trauma) i.e., Traumatic Brain Injury [TBI])			
<p>There was one RCT (<i>fair</i> quality) and one comparative observational study (<i>fair</i> quality) with a total of 79 patients who received rFVIIa. This yielded low strength of evidence with fair applicability for treatment use in the population targeted—patients with intracranial hemorrhage secondary to TBI who were not on anticoagulation therapy.</p> <p>Regarding the benefits and harms of rFVIIa, our findings include:</p> <ul style="list-style-type: none"> There was no effect of rFVIIa on mortality (Figure C) or thromboembolic event rate (Figure D). 	Yes.	No	

<ul style="list-style-type: none"> • rFVIIa use vs. usual care had no effect on hematoma growth but, in the one study that evaluated it, reduced the time to neurosurgical intervention (e.g., by normalizing the INR to an acceptable level). • Current evidence of low strength is too limited to compare harms and benefits. <p>Regarding subpopulations of patients, our findings include:</p> <ul style="list-style-type: none"> • Patients with coagulopathy may have increased benefits. • Patients experiencing blunt trauma to the cerebral vessels may have a greater risk of thromboembolic events when rFVIIa is used. • There was inadequate information available to assess the effect of rFVIIa dosage. 			
Key Question 4a. Use of rFVIIa for Selected Indications in Patient With/Undergoing Liver Transplantation			
<p>There were four RCTs (two <i>fair</i> quality, two <i>poor</i> quality) and one comparative observational study (<i>fair</i> quality) with 215 patients who received prophylactic rFVIIa at initiation of liver transplantation. This yielded low strength of evidence with fair applicability for prophylactic use in the population targeted—patients with cirrhosis of Child’s class B or C. Regarding the benefits and harms of rFVIIa, our findings include:</p> <ul style="list-style-type: none"> • There was no effect of rFVIIa use on mortality (Figure C) or thromboembolism (Figure D) relative to usual care. • There was a trend across studies toward reduced RBC transfusion requirements with rFVIIa use vs. usual care. • Neither operating room time nor ICU length of stay were reduced with rFVIIa use compared to usual care. • Current evidence of low strength is too limited to compare harms and benefits. 	<p>Yes. Only one systematic review published since then:</p> <p>Chavez-Tapia NC et al. Prophylactic activated recombinant factor VII in liver resection and liver transplantation: systematic review and meta-analysis. PLoS One. 2011;6(7):e22581</p>	No	

<p>Regarding subpopulations of patients, our findings include:</p> <ul style="list-style-type: none"> Patients who refuse blood product transfusions, such as Jehovah's Witnesses, may experience benefits from rFVIIa use, but there was inadequate information to assess this. There was inadequate information available to assess the effect of rFVIIa dosage. 			
Key Question 4b.i. Use of rFVIIa for Selected Indications in Patient With/Undergoing Cardiac Surgery (Adult Cardiac Surgery)			
<p>There were two RCTs (one <i>good</i> quality, one <i>fair</i> quality) and four comparative observational studies (two <i>good</i> quality, two <i>fair</i> quality) with 251 patients receiving rFVIIa. One of the RCTs assessed prophylactic rFVIIa use, whereas the rest of the studies evaluated treatment use. These yielded a moderate strength of evidence for the outcome of thromboembolic events but a low strength of evidence for the remainder of the outcomes. The studies had fair applicability for rFVIIa use in the population targeted—patients undergoing cardiac surgery, including straightforward procedures (e.g., isolated coronary artery bypass grafting [CABG]) and more complex procedures (e.g., ascending aortic dissection repair).</p> <p>In all cases where meta-analyses were performed, the results of the risk difference and arcsine metrics were consistent. The risk difference summary statistics are reported below. Regarding the benefits and harms of rFVIIa, our findings include:</p> <ul style="list-style-type: none"> There was no effect of rFVIIa on mortality (risk difference 0.007; 95 percent CI -0.049 to 0.063; <i>p</i> value for the <i>Q</i> statistic is 0.63) (also see Figure C). rFVIIa use was associated with a higher thromboembolic event rate (risk difference 0.053; 95 percent CI 0.01 to 0.096; <i>p</i> value for the <i>Q</i> statistic is 0.99) (also see Figure D). RBC transfusion needs were possibly reduced with rFVIIa, but the trend was only apparent across the 	<p>Yes.</p> <p>Only one retrospective cohort study published since the review:</p> <p>Uber WE et al. Administration of recombinant activated factor VII in the intensive care unit after complex cardiovascular surgery: clinical and economic outcomes. J Thorac Cardiovasc Surg. 2011 Jun;141(6):1469-77</p>	No	

<p>higher quality studies that reported on this outcome (one RCT and one <i>good</i> quality cohort study, $p = 0.11$ and $p < 0.001$, respectively; the other RCT only reported on total transfusion needs, which were significantly reduced). The findings across the <i>fair</i> quality observational studies were conflicting.</p> <ul style="list-style-type: none"> • There were conflicting results among studies regarding ICU length of stay. • Current evidence of moderate strength (for thromboembolic events) or low strength (for all other outcomes) suggests that neither benefits nor harms substantially exceed each other. <p>Regarding subpopulations of patients, our findings include:</p> <ul style="list-style-type: none"> • There was a suggestion that earlier treatment use of rFVIIa increases its benefits. • There was inadequate information available to assess the effect of rFVIIa dosage. 			
Key Question 4b.ii . Use of rFVIIa for Selected Indications in Patient With/Undergoing Cardiac Surgery (Pediatric Cardiac Surgery)			
<p>A total of 40 patients received rFVIIa prophylaxis in one <i>poor</i> quality RCT, (the only included study). This yielded an insufficient strength of evidence and fair applicability for the population targeted—infant patients with congenital heart defects requiring surgical repair. Regarding the benefits and harms of rFVIIa, our findings include:</p> <ul style="list-style-type: none"> • There were no data reported on mortality from the single RCT available. • The effect of rFVIIa on thromboembolic events cannot be discerned from existing data due to limited events. RBC transfusion requirements demonstrated a nonsignificant decrease among patients receiving rFVIIa vs. usual care: 77 mL and 127 mL, respectively, $p = 0.15$. • Time from end of cardiopulmonary bypass to chest 	Yes	No	

<p>closure was increased significantly in rFVIIa patients: 99 minutes (SD = 27) for rFVIIa vs. 55 minutes (SD = 29) for usual care, $p = 0.03$.</p> <ul style="list-style-type: none"> Current evidence is insufficient for comparing harms and benefits. <p>Regarding subpopulations of patients, our findings include:</p> <ul style="list-style-type: none"> Patients on extracorporeal membrane oxygenation (ECMO) may be more likely to experience thromboembolic events. There was inadequate information available to assess the effect of rFVIIa dosage. 			
Key Question 4c. Use of rFVIIa for Selected Indications in Patient With/Undergoing Prostatectomy			
<p>There was one <i>fair</i>-quality RCT on prophylactic use of rFVIIa in 24 patients undergoing prostatectomy. This yielded an insufficient strength of evidence and poor applicability for the population targeted—patients undergoing retropubic prostatectomy for prostate cancer or benign hyperplasia but not on anticoagulation therapy. These data have limited relevance given the major changes in usual care since the RCT was performed and the lack of reported use of rFVIIa for prostatectomy in the United States in 2008. Regarding the benefits and harms of rFVIIa, our findings include:</p> <ul style="list-style-type: none"> Mortality and thromboembolic events could not be evaluated due to limited reported events (one thromboembolic event in a rFVIIa patient, no deaths in either group). RBC transfusion needs were significantly decreased by rFVIIa, with a possible greater effect at higher doses: 1.5 units (SD = 0.4) for usual care, 0.6 units (SD = 0.3) for 20 mcg/kg, 0 (0) for 40 mcg/kg ($p < 0.01$). Operating room time was significantly reduced with 	Yes	No	

<p>rFVIIa (122 minutes [SD = 17] for rFVIIa vs. 180 minutes [SD = 16] for usual care, $p < 0.01$).</p> <ul style="list-style-type: none"> Current evidence is insufficient for comparing harms and benefits. <p>Regarding subpopulations of patients, our findings include:</p> <ul style="list-style-type: none"> There was inadequate information available to assess the effect of rFVIIa dosage on outcomes other than RBC transfusion requirements. 			
<p>Conclusions</p> <p>Available evidence on off-label rFVIIa use is limited across a wide spectrum of off-label indications. Considering the evidence as a whole, off-label rFVIIa may provide some benefit for certain clinical indications, but this conclusion is largely based on indirect outcomes that have an uncertain relationship to patient survival or functional status. Of the indications we studied, the benefit-to-risk ratio may be more favorable for body trauma than for other indications, because its use may reduce the occurrence of acute respiratory distress syndrome (ARDS); however, the strength of evidence is low for this as well as most other outcomes, which precludes definitive conclusions. Available evidence does not indicate that use of off-label rFVIIa reduces mortality or improves other direct outcomes for the indications we studied. Thromboembolic events are increased by use of rFVIIa in intracranial hemorrhage and adult cardiac surgery. Despite this state of evidence, in-hospital, off-label cases of rFVIIa use have increased in the last decade, particularly for cardiac surgery, trauma, and intracranial hemorrhage.</p>	<p>Yes</p> <p>New articles that I am aware of are: Char M. et al. (2011) Off-Label Recombinant Factor VIIa Use and Thrombosis in Children: A Multi-Center Cohort Study. <i>The Journal of Pediatrics</i> 158:5, 820-825.e1</p>	<p>No</p> <p>Cochrane review done on the use of rFVIIa for bleeding in non-hemophiliac patients:</p> <p>Lin Y et al. Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia. Cochrane Database Syst Rev. 2011 Feb 16;(2):</p>	
CER=comparative effectiveness review;			

Comparative Effectiveness of In-Hospital Use of Recombinant Factor VIIa for Off-Label Indications vs. Usual Care

AHRQ Publication No. 10-EHC030-EF May 2010

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Responses from expert # 2

Conclusions from CER (executive summary)	Is the conclusion(s) in this CER still valid? (Yes/No/Don't know)	Are you aware of any new evidence that is sufficient to invalidate the finding(s) in CER? (Yes/No/Don't know) If yes, please provide references	Comments
Key Question 1. Indications, Populations, and Characteristics of Comparative Studies of Off-Label rFVIIa Use			
Signal detection was not applicable for this question.			
Key Question 2. Use of rFVIIa for Selected Indications in Patient With/Undergoing Intracranial Hemorrhage			
For intracranial hemorrhage, because there were indications in the literature regarding a possible dose–response relationship between rFVIIa and certain outcomes (e.g., thromboembolic events) and multiple doses of rFVIIa were analyzed in each RCT, we chose <i>a priori</i> to analyze the data according to low-, medium-, and high-dose rFVIIa groups, defined as less than or equal to 40 µg/kg, greater than 40 but less 120 µg/kg, and at least 120 µg/kg, respectively. There were ES-9 four RCTs (two <i>good</i> quality, two <i>fair</i> quality) and one small comparative observational studies (<i>fair</i> quality) that assessed 968 patients who received rFVIIa. The RCTs evaluated patients who were not on oral anticoagulation therapy (OAT) and had intracerebral hemorrhage (ICH), whereas the observational study examined patients on OAT who could have experienced ICH or other forms of intracranial hemorrhage (e.g., subdural bleeding). These studies yielded moderate strength of evidence with good applicability for treatment use in the population targeted by the RCTs—patients with intracerebral hemorrhage who were not on anticoagulation therapy. In all cases	No	Regarding OAT, I believe there is now substantial evidence that rFVIIa will rapidly reverse anticoagulation in these patients, although documentation of changed outcomes is still needed. Look for the work of Stein, et al. in the J of Trauma. At least one of these papers described an economic benefit to the use of FVIIa in patients with TBI.	

<p>where meta-analyses were performed, the results of the risk difference and arcsine metrics were consistent. The risk difference summary statistics are reported below. Regarding the benefits and harms of rFVIIa, our findings include: (Figure C).</p> <ul style="list-style-type: none"> • There was no effect of rFVIIa on mortality (risk difference: low-dose group: 0.031 (95 percent CI -0.086 to 0.024), medium-dose group: 0.020 (95 percent CI -0.076 to 0.036), high-dose group: 0.027 (95 percent CI -0.121 to 0.068); <i>p</i> value of the <i>Q</i> statistic for all risk differences is 0.248) (also see Figure C: each circle represents a study; larger circles correspond to larger studies; shaded circles represent studies on treatment use of rFVIIa, and white circles represent studies on prophylactic use of rFVIIa). rFVIIa use also did not reduce the rate of poor functional outcome as measured on the modified Rankin Scale (risk difference: low-dose group: 0.024 (95 percent CI -0.093 to 0.045), medium-dose group: 0.029 (95 percent CI -0.099 to 0.041), high-dose group: 0.040 (95 percent CI -0.154 to 0.075); <i>p</i> value of the <i>Q</i> statistic for all risk differences is 0.088). • There was an increased rate of arterial thromboembolic events with rFVIIa use vs. usual care for the medium- and high-dose groups (risk difference: low-dose group: 0.025 (95 percent CI -0.004 to 0.053), medium-dose group: 0.035 (95 percent CI 0.008 to 0.062), high-dose group: 0.063 (95 percent CI 0.011 to 0.063); <i>p</i> value of the <i>Q</i> statistic for all risk differences is 0.277) (see Figure D). • rFVIIa use significantly decreased the percent relative hematoma expansion (standardized mean difference: low-dose group: 0.146 (95 percent CI -0.291 to -0.001), medium-dose group: 0.240 (95 percent CI -0.385 to 0.095), high-dose group: 0.334 (95 percent CI -0.579 to -0.090); <i>p</i> value of the <i>Q</i> 			
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<p>statistic for all risk differences is 0.840).</p> <ul style="list-style-type: none"> • In summary, current evidence of moderate strength suggests that neither benefits nor harms substantially exceed each other for rFVIIa use in the ICH subgroup of intracranial hemorrhage. <p>Regarding subpopulations of patients, our findings include:</p> <ul style="list-style-type: none"> • Earlier administration of rFVIIa for ICH may increase benefits, but this finding may be confounded by earlier CT scanning among these patients. • There may be greater benefits in younger patients with smaller initial hematoma size. • There was no evidence of a dose effect for any endpoint. • Evolution of intracranial hemorrhage management may reduce the size of the population in which there is a potential benefit of rFVIIa. • There were insufficient studies to assess the impact of rFVIIa on patients taking oral anticoagulation therapy 			
Key Question 3a. Use of rFVIIa for Selected Indications in Patient With/Undergoing Massive Bleeding from Trauma (Body Trauma)			
<p>There were two RCTs (both published in a single paper and of <i>fair</i> quality) and three comparative observational studies (all <i>fair</i> quality) with 267 patients who received rFVIIa. This yielded low strength of evidence with fair applicability for treatment use in the population targeted—patients with blunt or penetrating trauma who were not censored for early in-hospital death (defined as 24 hours or 48 hours depending on the study). Regarding the benefits and harms of rFVIIa, our findings include:</p> <ul style="list-style-type: none"> • There was no effect of rFVIIa on mortality (Figure C) or thromboembolism (Figure D) relative to usual care. • For acute respiratory distress syndrome, the blunt trauma RCT demonstrated a significant reduction with rFVIIa use vs. usual care, while the remaining two studies that evaluated this outcome (the penetrating trauma RCT and one observational 	<p>Yes. The reduction of transfusion requirements in particular has been verified.</p>	<p>See above. The CONTROL data greatly expanded these findings.</p>	

<p>study) showed a nonsignificant trend in the same direction.</p> <ul style="list-style-type: none"> There was conflicting evidence regarding RBC transfusion requirements. These were significantly decreased among patients receiving rFVIIa vs. usual care in one RCT ($p = 0.02$) and nonsignificantly decreased in the other RCT ($p = 0.10$). In contrast, the one observational study that independently measured this found a significant increase in RBC transfusion requirements ($p = 0.02$). Overall, current evidence of low strength suggests the potential for benefit and little evidence of increased harm. <p>Regarding subpopulations of patients, our findings include:</p> <ul style="list-style-type: none"> Patients with blunt trauma may experience greater benefits than those with penetrating trauma. Greater benefits are also possible in patients with higher baseline pH, shorter time to administration, and higher platelet counts. There was inadequate information available to assess the effect of rFVIIa dosage. 			
Key Question 3b. Use of rFVIIa for Selected Indications in Patient With/Undergoing Massive Bleeding from Trauma (Brain Trauma) i.e., Traumatic Brain Injury [TBI])			
<p>There was one RCT (<i>fair</i> quality) and one comparative observational study (<i>fair</i> quality) with a total of 79 patients who received rFVIIa. This yielded low strength of evidence with fair applicability for treatment use in the population targeted—patients with intracranial hemorrhage secondary to TBI who were not on anticoagulation therapy.</p> <p>Regarding the benefits and harms of rFVIIa, our findings include:</p> <ul style="list-style-type: none"> There was no effect of rFVIIa on mortality (Figure C) or thromboembolic event rate (Figure D). rFVIIa use vs. usual care had no effect on hematoma 	Yes	Regarding OAT, I believe there is now substantial evidence that rFVIIa will rapidly reverse anticoagulation in these patients, although documentation of changed outcomes is still needed. Look for the work of Stein, et al. in the J of Trauma. At least one of these papers described an economic benefit to the use of FVIIa in patients with TBI.	

<p>growth but, in the one study that evaluated it, reduced the time to neurosurgical intervention (e.g., by normalizing the INR to an acceptable level).</p> <ul style="list-style-type: none"> • Current evidence of low strength is too limited to compare harms and benefits. <p>Regarding subpopulations of patients, our findings include:</p> <ul style="list-style-type: none"> • Patients with coagulopathy may have increased benefits. • Patients experiencing blunt trauma to the cerebral vessels may have a greater risk of thromboembolic events when rFVIIa is used. • There was inadequate information available to assess the effect of rFVIIa dosage. 			
Key Question 4a. Use of rFVIIa for Selected Indications in Patient With/Undergoing Liver Transplantation			
<p>There were four RCTs (two <i>fair</i> quality, two <i>poor</i> quality) and one comparative observational study (<i>fair</i> quality) with 215 patients who received prophylactic rFVIIa at initiation of liver transplantation. This yielded low strength of evidence with fair applicability for prophylactic use in the population targeted—patients with cirrhosis of Child’s class B or C. Regarding the benefits and harms of rFVIIa, our findings include:</p> <ul style="list-style-type: none"> • There was no effect of rFVIIa use on mortality (Figure C) or thromboembolism (Figure D) relative to usual care. • There was a trend across studies toward reduced RBC transfusion requirements with rFVIIa use vs. usual care. • Neither operating room time nor ICU length of stay were reduced with rFVIIa use compared to usual care. • Current evidence of low strength is too limited to compare harms and benefits. <p>Regarding subpopulations of patients, our findings</p>	No	<p>My sense is that use in this area has plateaued at a relatively infrequent rate of use, primarily for rescue.</p>	

<p>include:</p> <ul style="list-style-type: none"> • Patients who refuse blood product transfusions, such as Jehovah's Witnesses, may experience benefits from rFVIIa use, but there was inadequate information to assess this. • There was inadequate information available to assess the effect of rFVIIa dosage. 			
Key Question 4b.i. Use of rFVIIa for Selected Indications in Patient With/Undergoing Cardiac Surgery (Adult Cardiac Surgery)			
<p>There were two RCTs (one <i>good</i> quality, one <i>fair</i> quality) and four comparative observational studies (two <i>good</i> quality, two <i>fair</i> quality) with 251 patients receiving rFVIIa. One of the RCTs assessed prophylactic rFVIIa use, whereas the rest of the studies evaluated treatment use. These yielded a moderate strength of evidence for the outcome of thromboembolic events but a low strength of evidence for the remainder of the outcomes. The studies had fair applicability for rFVIIa use in the population targeted—patients undergoing cardiac surgery, including straightforward procedures (e.g., isolated coronary artery bypass grafting [CABG]) and more complex procedures (e.g., ascending aortic dissection repair).</p> <p>In all cases where meta-analyses were performed, the results of the risk difference and arcsine metrics were consistent. The risk difference summary statistics are reported below. Regarding the benefits and harms of rFVIIa, our findings include:</p> <ul style="list-style-type: none"> • There was no effect of rFVIIa on mortality (risk difference 0.007; 95 percent CI -0.049 to 0.063; <i>p</i> value for the <i>Q</i> statistic is 0.63) (also see Figure C). • rFVIIa use was associated with a higher thromboembolic event rate (risk difference 0.053; 95 percent CI 0.01 to 0.096; <i>p</i> value for the <i>Q</i> statistic is 0.99) (also see Figure D). • RBC transfusion needs were possibly reduced with rFVIIa, but the trend was only apparent across the higher quality studies that reported on this outcome 	No	<p>My sense is that use in this area has plateaued at a relatively infrequent rate of use, primarily for rescue.</p>	

<p>(one RCT and one <i>good</i> quality cohort study, $p = 0.11$ and $p < 0.001$, respectively; the other RCT only reported on total transfusion needs, which were significantly reduced). The findings across the <i>fair</i> quality observational studies were conflicting.</p> <ul style="list-style-type: none"> • There were conflicting results among studies regarding ICU length of stay. • Current evidence of moderate strength (for thromboembolic events) or low strength (for all other outcomes) suggests that neither benefits nor harms substantially exceed each other. <p>Regarding subpopulations of patients, our findings include:</p> <ul style="list-style-type: none"> • There was a suggestion that earlier treatment use of rFVIIa increases its benefits. • There was inadequate information available to assess the effect of rFVIIa dosage. 			
Key Question 4b.ii . Use of rFVIIa for Selected Indications in Patient With/Undergoing Cardiac Surgery (Pediatric Cardiac Surgery)			
<p>A total of 40 patients received rFVIIa prophylaxis in one <i>poor</i> quality RCT, (the only included study). This yielded an insufficient strength of evidence and fair applicability for the population targeted—infant patients with congenital heart defects requiring surgical repair. Regarding the benefits and harms of rFVIIa, our findings include:</p> <ul style="list-style-type: none"> • There were no data reported on mortality from the single RCT available. • The effect of rFVIIa on thromboembolic events cannot be discerned from existing data due to limited events. RBC transfusion requirements demonstrated a nonsignificant decrease among patients receiving rFVIIa vs. usual care: 77 mL and 127 mL, respectively, $p = 0.15$. • Time from end of cardiopulmonary bypass to chest closure was increased significantly in rFVIIa 	No		

<p>patients: 99 minutes (SD = 27) for rFVIIa vs. 55 minutes (SD = 29) for usual care, $p = 0.03$.</p> <ul style="list-style-type: none"> Current evidence is insufficient for comparing harms and benefits. <p>Regarding subpopulations of patients, our findings include:</p> <ul style="list-style-type: none"> Patients on extracorporeal membrane oxygenation (ECMO) may be more likely to experience thromboembolic events. There was inadequate information available to assess the effect of rFVIIa dosage. 			
Key Question 4c. Use of rFVIIa for Selected Indications in Patient With/Undergoing Prostatectomy			
<p>There was one <i>fair</i>-quality RCT on prophylactic use of rFVIIa in 24 patients undergoing prostatectomy. This yielded an insufficient strength of evidence and poor applicability for the population targeted—patients undergoing retropubic prostatectomy for prostate cancer or benign hyperplasia but not on anticoagulation therapy. These data have limited relevance given the major changes in usual care since the RCT was performed and the lack of reported use of rFVIIa for prostatectomy in the United States in 2008. Regarding the benefits and harms of rFVIIa, our findings include:</p> <ul style="list-style-type: none"> Mortality and thromboembolic events could not be evaluated due to limited reported events (one thromboembolic event in a rFVIIa patient, no deaths in either group). RBC transfusion needs were significantly decreased by rFVIIa, with a possible greater effect at higher doses: 1.5 units (SD = 0.4) for usual care, 0.6 units (SD = 0.3) for 20 mcg/kg, 0 (0) for 40 mcg/kg ($p < 0.01$). Operating room time was significantly reduced with rFVIIa (122 minutes [SD = 17] for rFVIIa vs. 180 	No	No follow-up to the original publication because – in the US at least – there is much less risk of transfusion in this population, and massive transfusion is very unlikely.	

<p>minutes [SD = 16] for usual care, $p < 0.01$).</p> <ul style="list-style-type: none"> Current evidence is insufficient for comparing harms and benefits. <p>Regarding subpopulations of patients, our findings include:</p> <ul style="list-style-type: none"> There was inadequate information available to assess the effect of rFVIIa dosage on outcomes other than RBC transfusion requirements. 			
<p>Conclusions</p> <p>Available evidence on off-label rFVIIa use is limited across a wide spectrum of off-label indications. Considering the evidence as a whole, off-label rFVIIa may provide some benefit for certain clinical indications, but this conclusion is largely based on indirect outcomes that have an uncertain relationship to patient survival or functional status. Of the indications we studied, the benefit-to-risk ratio may be more favorable for body trauma than for other indications, because its use may reduce the occurrence of acute respiratory distress syndrome (ARDS); however, the strength of evidence is low for this as well as most other outcomes, which precludes definitive conclusions. Available evidence does not indicate that use of off-label rFVIIa reduces mortality or improves other direct outcomes for the indications we studied. Thromboembolic events are increased by use of rFVIIa in intracranial hemorrhage and adult cardiac surgery. Despite this state of evidence, in-hospital, off-label cases of rFVIIa use have increased in the last decade, particularly for cardiac surgery, trauma, and intracranial hemorrhage.</p>	Yes	Look for recent publications examining use in obstetrical hemorrhage and other hemorrhagic conditions.	
CER=comparative effectiveness review;			